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Hormonal Relationships and Applications IN THE Production of Meats, Milk, and Eggs

A Report of the
Committee on Animal Nutrition

By Sykes

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HORMONAL RELATIONSHIPS AND APPLICATIONS IN THE PRODUCTION OF MEATS, MILK, AND EGGS

A Report of the
Committee on Animal Nutrition

Prepared by the
SUBCOMMITTEE ON HORMONES

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HORMONAL RELATIONSHIPS AND APPLICATIONS IN THE PRODUCTION OF MEATS, MILK, AND EGGS*

INTRODUCTION

Evidence has been accumulating over a period of many years and particularly during the past twenty years concerning the fundamental role of the glands of internal secretion and the hormones they produce on various functions of the animal body. Certain of these hormones have marked effects on rates of growth and fattening, on growth of the mammary gland, on the initiation and maintenance of milk production, and on the control of reproductive processes. Many of the details concerning the mechanisms by which they exert these effects and the interrelationships that exist between the several glands are still not well defined. That the hormones exert sizable effects on processes which are of interest to the producers of livestock and poultry is, however, quite clear, and the application of these principles to the production of meats, milk, and eggs has intrigued both the research worker and the producer.

Until recent years possible applications of these findings have been handicapped by the cost of the hormones involved, the necessity for frequent injections, and lack of methods for controlling the activity of the glands that secrete hormones. Some of these objections have now been eliminated to a certain extent.

In 1938 Dodds et al. (9) prepared and described a synthetic estrogenic compound, diethylstilbestrol. Subsequently, hexestrol and other synthetic estrogens have been produced. These synthetic estrogens are often considerably more potent when given orally than the naturally occurring estrogens (10, 20) and can be obtained at a small fraction of the cost of the natural estrogens.

At about the same time, Ludwig and von Mutzenbecher (11, 12) prepared an iodinated casein from which they isolated thyroxine, the hormone of the thyroid gland. The iodination process was subsequently improved by Reineke and Turner (14, 15, 16, 17) and an iodinated casein containing thyroxine and with an activity several times greater than dried thyroid gland can now be produced. A variety of proteins may be iodinated in this way, and the thyroidal potency of these products is quite variable. The term thyroprotein† would include all these. In the present report, however, this term is used to denote iodinated casein having essentially the thyroidal potency of the preparations of Reineke and Turner. The apparent thyroxine content of this preparation was originally stated to be about 3 per cent. The most recent and more nearly correct figure suggests that iodinated caseins contain 0.3 to 0.7 per cent thyroxine (6, 19).

Thyroprotein has been shown to be about $\frac{1}{20}$ as effective when given orally as when it is injected (18). If the value of 0.3 to 0.7 per cent for the thyroxine content of thyroprotein is applied to the data of Bailey et al. (4), the efficiency of utilization of the thyroxine in iodinated casein is the same as that for L-thyroxine when both are given orally. The biologically active component of the thyroid

* This report was prepared by a subcommittee of the Committee on Animal Nutrition of the Agricultural Board, National Research Council, composed of J. F. Sykes (Chairman), Bureau of Dairy Industry, U. S. D. A.; F. N. Andrews, Purdue University; F. W. Hill, Cornell University; F. W. Lorenz, University of California; J. W. Thomas, Bureau of Dairy Industry, U. S. D. A.; and C. F. Winchester, Bureau of Animal Industry, U. S. D. A. The literature published prior to July 1952 forms the basis for the report.

† Thyroprotein is manufactured in the United States under the trade name "Protamone." As such it is available to manufacturers for inclusion in feeds where this is permitted.

gland and thyroprotein, L-thyroxine, has recently been synthesized (5, 7, 8) and the cost is said to be less than for iodinated casein of equivalent biological potency.

During the same period a group of drugs was discovered which suppress the secretion of the thyroid gland (1, 2, 13). Since this action is accompanied by an enlargement of the thyroid gland, these compounds are called goitrogens. They are also known as antithyroid compounds because of their inhibition of thyroid secretion. This group of compounds includes thiourea, thiouracil and its derivatives, sulfonamides, and thiobarbital. The effects of these several compounds differ both within and between species.

As a result of these developments there are now available relatively inexpensive sources of synthetic estrogens and of thyroxine or thyroxine-containing materials which can be used to duplicate the action of naturally occurring estrogens or thyroid hormone. The goitrogens provide materials with which the activity of the thyroid gland may be controlled.

Within these areas of study considerable possibility exists that physiological processes of livestock and poultry may be regulated for more efficient production of animal products such as meats, milk, and eggs. Some aspects of this work were reviewed by Blaxter et al. (3) in 1949. It should not be inferred that applications of estrogen and thyroid physiology are the only areas in which possibilities for improvement exist. New developments are continually occurring. Progesterone and the adrenal cortical and pituitary hormones are now more available and their effects on farm animals are being studied. These and other hormones will only be referred to as they pertain to the main topics chosen for discussion or as they indicate lines of study for further work. Similarly the great body of data which exists concerning the role of hormones in reproduction and their possible use is not discussed except in a few instances. The emphasis on estrogens and on thyroidally active materials in the present report is largely a result of the fact that practices based on these aspects of physiology are now being introduced into animal husbandry.

The use of any of these compounds involves many factors that must be considered before successful application may be made to livestock or poultry production. These include complex physiological reactions and adjustments and problems of management, of economics, and of consumer acceptance of the product, as discussed in detail in succeeding sections of this report. Whether sufficient control of all these factors can be obtained under commercial conditions is a matter of some speculation. Thus it is perhaps not surprising that wider commercial acceptance has not taken place. It is perhaps significant, however, that, in those instances where considerable commercial use of certain products is being made, the conditions necessary for such application have been rather thoroughly investigated. It appears probable that continuing research may not only improve presently accepted uses but may make additional commercial applications of other products possible.

Another major aspect of hormonal applications is the problem of residues of these compounds remaining in products used for human consumption. In the applications which have so far been studied there seems to be little likelihood that any harmful effects in humans will result from the occasional consumption of the small amounts of such residues that have been shown to remain in such foods. The possibility that physiologically effective amounts of residues may remain in the product in any new application or modification of treatment must not be ignored, however. Moreover, if these applications become more generally used commercially, humans may be exposed almost continuously to small amounts of residues. The possible cumulative effects of such exposure over long periods of time are undetermined.

The use of these or any new compounds

must be subject to authorization by law wherever the food produced is to be used for human consumption. All proposals for such use must be submitted to the appropriate governmental agency. Proof must be furnished that foods will not be harmful when produced under the proposed conditions. Regulations vary, depending on country of origin. Permissions for or prohibitions against the use of the several products are listed in the appropriate sections of this report. Only specific permissions or prohibitions are listed, and it should not be assumed that prohibitions exist against the use of any given compound unless such is stated although all proposals other than those listed are subject to review.

Only two procedures have had any sizable commercial acceptance in the United States. These are the use of diethylstilbestrol for fattening poultry and the inclusion of thyroprotein in feeds for dairy cattle. It is permissible to use thiouracil and thyroprotein for both poultry and swine. Neither of these products has been used to any extent commercially, although the inclusion of thiouracil in feeds for fattening swine and young meat birds appears to be a useful procedure under proper conditions. Similarly, the use of diethylstilbestrol seems to offer possibilities for increasing rate of gain and feed efficiency in both beef cattle and lambs. These are the only procedures which can be recommended on the basis of present information. In the Dominion of Canada none of these procedures have been authorized although the only direct prohibition concerns the use of estrogens for fattening poultry. In Great Britain there is no prohibition of the use of estrogens for poultry although this procedure has had only limited application there. The use of thyroprotein in Great Britain is restricted to experimental studies.

In the succeeding sections of this report a detailed account of the physiological and experimental background pertaining to the applications of certain aspects of endocrine physiology in livestock and poultry production is presented. These discussions are the basis for the recommendations which can be made at the present time and provide a background for future research or more extensive application. The arrangement of the several topics, in which the discussion is centered around the uses of particular compounds as they apply to the several species or to specific applications, was chosen for purposes of clarity and to facilitate the use of this information by those interested in special phases of livestock and poultry production. A general summary and the recommendations which can be made concerning particular applications are included in the appropriate sections.

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THE USE OF ESTROGENS FOR FATTENING POULTRY

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Estrogenic Effects in Birds

The effects of estrogens on lipid metabolism in birds are well known, but in many respects are not well understood. The increases in the cholesterol, phospholipid, and triglyceride contents of the blood following estrogen supply (whether by the active ovary or by administration) have been frequently described (27, 31, 32, 44, 45, 48, 49, 50, 58, 60, 61, 79, 80, 85, 87, 88, 89, 94, 95, 114, 116, 117, 118, 121, 142, 149, 153, 154, 155). The response is rapid; increased lipid levels have been observed as early as 12 hours after subcutaneous administration of natural or synthetic estrogens (89, 142), and they wane almost as fast after withdrawal of the estrogen supply.

Few of the data so far obtained throw light on the mechanisms involved. That the increase does not depend on dietary fat (or on any nutritional source, for that matter) has been demonstrated by the estrogen-induced lipemias produced after withholding food for 48 hours (154, 155) and for several weeks (97). By use of P^{32} increased rate of phospholipid synthesis in the liver was observed to follow intramuscular injection of diethylstilbestrol and to precede the development of lipemia (142). Studies of birds in puberty (27) have shown that fat deposition in the liver may also precede the development of lipemia. Both observations suggest that blood fat may be derived from lipids synthesized in the liver. After injection of inorganic P^{32}, diethylstilbestrol-treated and control birds had similar specific activity of plasma phospholipid, indicating that the turnover rate is the same under both conditions but that treated birds were adding more new phospholipid per unit time to the circulation (50).

The role of other endocrine glands in the lipemic response to estrogen is not yet thoroughly understood. The full lipid response to estrogen has been obtained in pigeons deprived of their pituitary glands, adrenals, pancreas, parathyroids, or testes (121). Androgens, progesterone, desoxycorticosterone acetate, and insulin have no consistent effect on blood lipids (45, 121), nor have pituitary preparations except those containing gonadotropins, and then only in birds with intact ovaries. Thyroid preparations administered simultaneously with estrogens reduce or abolish the response of blood lipids but not of oviduct growth (47, 48, 97, 101). Decreasing the thyroid activity will itself produce a moderate increase in blood cholesterol (48) and a moderate increase in all blood lipid constituents has been observed in ducks after thyroidectomy (14).

Bird (15) observed a marked reduction in heart rate and a statistically increased rate of feed consumption over that expected from the observed rate of gain, following treatment with estrogen. He believed that these effects were probably mediated by adrenal enlargement and consequent inhibition of the thyroid, and stated (19) that a low rate of "metabolic efficiency" is requisite for the deposition of fat. However, while heart rate tends to parallel metabolic rate, the correlation is not close enough to make possible the prediction of one from the other (152). Also, where fat is being deposited, as here, less total gain per unit of feed consumed is to be expected because of the relatively high caloric concentration of adipose tissue. Unfortunately, conclusive direct estimates of the effect of estrogens on heat production in fattening birds have not been made. The existing indirect evidence (10, 42, 43, 103, 107, 108, 127, 128, 152), and especially that in the recent observation (46) that administration of dianisylhexene de-

creases the rate of turnover of I^{131} in chicks, is only suggestive, and a depressing effect of estrogen on metabolic rate cannot be considered proved. Also, if the effect does exist it is probably relatively inconsequential for the fattening mechanism. The weight of evidence is that the effect of estrogen on lipid metabolism is direct, and although the thyroid undoubtedly plays a role in lipid metabolism, its relation to that of estrogen is not yet clear.

The relation of the blood-lipid level to the rate of fat synthesis or to fat deposition is also not entirely clear. Some degree of lipemia commonly accompanies endocrine-induced fattening of fowl, but the parallelism between the two effects is far from complete. Erratic fluctuations of successive blood samples from the same birds and different types of response to different kinds of estrogen treatment complicate interpretation. With some estrogens, at least, the threshold dosage for increased fat deposition is lower than for lipemia (95).

Estrogens produce numerous additional effects on birds, some of which have more significance in the practical results of estrogen treatment than have others. In addition to the lipemia there are striking increases in the plasma content of protein (29, 102, 123, 124), riboflavin (31, 32), and calcium and phosphorus (7, 11, 31, 32, 33, 47, 48, 58, 60, 61, 79, 80, 85, 101, 102, 109, 115, 118, 119, 120, 124, 153, 154, 155). The percentage volume of red cells tends to decrease (31).

Estrogen causes hyperossification of endosteal bone (25, 79, 80, 81, 82, 101, 109, 117, 119, 153, 155), and in pigeons, at least, this effect, as well as the production of calcemia, occurs in the absence of either the hypophysis or the parathyroids (119). Necessity for combined action of estrogen and androgen for hyperossification has been suggested (54, 56). Bone fragility has been observed during treatment with at least one estrogen (dianisylhexene) (51, 98, 144) and may follow prolonged diethylstilbestrol-pellet treatment in turkeys (97). Large doses of the former compound have caused spontaneous fractures of the tibia; moderate dosages have been followed by broken bones during killing and dressing. The fragile bones have normal percentage ash (98, 144), but reduction in the gross amount of cancellous bone has been observed (98). These effects, which appear to be paradoxical, may be due to bone resorption preceding hyperossification (25, 82) or to an apparent reversal of the latter with increasing total dosage of estrogen (81).

One of the most striking results of estrogen treatment is the extensive depression of the size and function of the testes—an effect that has given rise to the common misnomers for treated birds: "Chemical Capons" or "Caponettes." The birds' combs shrink to capon size and become pale and wrinkled. Aggressiveness diminishes; fighting and crowing cease. In chickens the masculine sex drive is usually also lost, and males assume the feminine sexual reaction, squatting readily when approached. Rarely, however, an opposite reaction has been observed. A treated flock suddenly becomes greatly excited sexually, and birds attempt to tread one another. In the author's experience instances of this reaction have been limited to flocks of mixed sex treated prior to six weeks of age. Spermatogenesis ceases, but only temporarily. Motile sperm can be obtained from cocks three to four weeks after withdrawal of the estrogen treatment (78, 99). Turkeys respond like chickens in regression of head furnishings and diminished fighting instinct, but in this species heightened sexual activity is the rule. In a treated flock most birds strut at any time of day; numerous attempts to tread may usually be observed, individual birds taking the male or female role indifferently or alternately.

The ovary, in contrast to the testes, is quite resistant to estrogen treatment. No reduction of egg production was observed in hens treated with various estrogens when the feed contained as much as 0.01 per cent of these substances or when a diethylstilbestrol pellet was im-

planted (99, 137). Double these levels failed to reduce ovulation rate, but 0.04 per cent of either dianisylhexene or dienestrol diacetate caused a significant reduction (1), and egg production was stopped with the former fed at 0.025 per cent (147). The turkey ovary is apparently somewhat more sensitive; implants of one or two pellets reduced but did not entirely stop egg production in two of three trials (111, 125, 135).

Estrogen produces an enlargement of the vent and spreading of the pubic bones such as normally occur in laying hens. Spontaneous prolapse has been reported once through the enlarged vents of treated cockerels (150); in hens, on the other hand, prolapse was aggravated by testosterone propionate but was unaffected by chronic treatment with diethylstilbestrol (26).

A single injection of estrogens in oil solution interrupts broodiness in hens. This treatment returns birds to egg production about as quickly, on the average, as use of broody coops. A 30-milligram dose was more uniformly successful than 15 milligrams for chickens (55); 200 milligrams were necessary for turkey hens (24).

Stimulation of oviduct growth is a well known function of estrogen. Dietary folic acid is necessary for the manifestation of this effect (65, 66). Oviduct function in mature hens is affected only slightly if at all by exogenous estrogens, as judged from the constitution of eggs laid during estrogen feeding (3).

Feather growth may be stimulated, and the development of new pin feathers may be inhibited, by estrogens (both effects tending to reduce the number of pin feathers on treated birds) (99). This effect has been more marked in turkeys than in chickens, and pinniness has been reduced in turkeys killed at ages varying from three to six months after treatment with various estrogens (35, 62, 67, 122, 146). The minimal effective dose for reducing pin feathers may be greater than that for fattening (146).

Improved skin texture is a definite consequence of estrogen treatment, presumably due to hypertrophy of the epidermal strata (16, 18). Dienestrol diacetate was more effective in producing this hypertrophy than dianisylhexene when both were administered by the oral route and in the same dosage (16).

Estrogenic Compounds, Routes of Administration, and Dosage for Fattening Poultry

Diethylstilbestrol as subcutaneously implanted pellets was the first compound and mode of administration to be studied for fattening, and the first to be used commercially. A single 12- to 15-milligram pellet is ordinarily used for growing birds; two are usually used for adult cocks, but adequate experimental data to justify this larger dosage have not been reported. The effects of the pellet begin to be noticeable within a week, but the treatment should be continued at least four weeks for satisfactory results; additional fattening may be obtained for six weeks or more.

In spite of their obvious importance, data on absorption are fragmentary. The rates of absorption of most commercial pellets are consistent with satisfactory fattening but are not necessarily optimal. Symptoms of apparent overdosage have occasionally been observed, and unabsorbed residues always remain in the dressed carcass. A pellet of pure diethylstilbestrol is absorbed at an average rate of 2 milligrams per week, approximately, for the first four weeks, and more slowly thereafter (90, 92, 93, 99, 148). The absorption rate may be greatly affected by the amount and nature of the excipient, but increasing the effective dosage to more than 2 milligrams per week has not increased the rate of fat deposition materially. A pellet containing 6 milligrams of diethylstilbestrol in an unknown carrier gave unsatisfactory results with turkeys (6) and with chickens (37), but in another trial with chickens (99) the results were equal to those obtained with 15-milligram pellets. Unab-

sorbed residues were not avoided. Pellets made with a sugar core coated with diethylstilbestrol (93) gave good responses and complete absorption in four weeks but have not been tested commercially. Solutions of diethylstilbestrol in oil (73, 99) have all been absorbed so rapidly that the resulting transitory effect fails to produce a useful response with a single injection. Aqueous suspensions of microcrystals (73, 98, 137, 138) are better but are also too rapidly absorbed. A recent paste suspension containing 15 milligrams diethylstilbestrol in a dose of 0.2 milliliters is completely absorbed in about three and a half weeks and is being favorably received commercially.

Parenteral administration of other estrogens for fattening has been little studied, and comparative potencies have been determined for only a few. Diethylstilbestrol, injected in oil, is more than twice as potent as estradiol benzoate or methoxy-bisdehydrodoisynolic acid (MDDA) for growth of the chick oviduct, and about eight times as potent as estrone. Estradiol esters were much more potent than the free diol (38, 39, 40, 41, 45, 104). When made into pellets and implanted, dimethylethers of the stilbene derivatives and dienestrol diacetate failed to absorb appreciably and gave little or no response as judged by comb-regression and lipogenesis. The response to dienestrol was good, but less than diethylstilbestrol (98). An excellent and unusually prolonged response was obtained with hexestrol pellets (23).

The convenience and labor-saving advantages of mixing the active material in the feed were so obvious that attempts to feed diethylstilbestrol were made almost from the start of these investigations. The early unsatisfactory results (see below) led to a search for new compounds of greater potency by the oral route. The relative ability of various estrogens to stimulate lipemia has been found to be closely related to their potency for oviduct growth (45) and attention was thereby immediately fixed on dimethylethers (69).

The three most frequently studied stilbenes are *a*, diethylstilbestrol, *b*, hexestrol, and *c*, dienestrol; their dimethylethers are respectively *d*, dianisylhexene, *e*, dianisylhexane, and *f*, dianisylhexadiene. These compounds exhibited the following decreasing order of potency when fed to chicks, as judged (with relatively inconsequential disagreement) from chick oviduct growth: *e*, *d*, *c*, *b*, *f*, *a* (71, 98, 106). The oral potency of dienestrol diacetate is identical with that of dienestrol (98). When assayed by testis suppression no distinction could be made between the potencies of compounds *b*, *c*, and *f*. The relative potencies of compounds *a*, *d*, and *e* were the same as when these were determined by the chick oviduct test. Striking reversals in this order were exhibited in the oral potency for oviduct growth in turkeys; dianisylhexane was almost nonpotent, and the complete series as above was *d*, *a*, *b*, *c*, *e*, *f* (71).

Jaap (71) studied a number of other compounds, most of which were too weak to warrant further consideration for fattening. One possible exception, triphenylchloroethylene, had an oral potency between compounds *b* and *c* for chickens and also fell in midseries for turkeys. Other estrogens tested by feeding for fattening include alpha estradiol, estriol, MDDA, and triphenylbromoethylene, but comparative oral potencies of these compounds for birds are not available.

Oral administration of *diethylstilbestrol* has generally been unsatisfactory (92, 93, 144), although improvements in carcass quality have been reported following either extended feeding with low dosages (21, 22, 141) or massive treatment for a shorter period (53). *Dienestrol diacetate* in the feed has given better results (15, 16, 52, 94, 95, 98). A moderately increased rate of fat deposition has been obtained by feeding this compound at levels between 0.002 per cent and 0.007 per cent of the ration. Between these limits the fattening occurs without measurable lipemia, and its rate has been independent of the level fed.

More than 0.007 per cent dienestrol diacetate in the feed has produced lipemia and a further increase in the rate of fat deposition. Extra fat deposition progresses steadily within either dosage range, and the desired amount of fattening may be obtained by controlling the length of the treatment period. Even the higher rate is a little slower than is the rate of fattening stimulated by a diethylstilbestrol pellet implant, however. Dianisylhexene has been studied extensively for fattening (15, 16, 51, 52, 53, 72, 74, 92, 94, 95, 98, 143, 144, 145). This compound stimulates fat deposition about as much as dienestrol diacetate at similar dosage levels, but exhibits certain striking disadvantages that contraindicate its use as a commercial fattening agent. These include its high tissue retention and slow toxicity. Dianisylhexene produces a much greater lipemia and has a lower lipemic threshold than dienestrol diacetate. Its fattening action and also its lipemic threshold are complicated by a resistance rapidly increasing with the age at which treatment is started (95). *Hexestrol* and *dianisylhexane* have been little investigated by feeding. Hexestrol produced more fattening than did diethylstilbestrol but somewhat less than dianisylhexane (95); the latter is comparable to dianisylhexene (92) but has the same disadvantage of high tissue retention (16).

Turkeys fatten less dramatically than chickens in response to estrogens. Diethylstilbestrol pellets increase the amount of fat deposited (6, 9, 62, 84, 91, 96, 99, 100, 110, 122, 130, 136), but not infrequently the extra fat is not enough to be apparent on visual inspection of the dressed carcass, especially as the birds approach maturity. One 15-milligram pellet has been suggested as the correct dosage for fryers and roaster hens and two for roaster toms, with treatment periods of three to four weeks (6, 100, 110, 130). Turkeys are quite sensitive to overdosage; more pellets or longer periods have conferred no advantage and have frequently had detrimental side effects.

Oral administration of estrogens to turkeys has led to some favorable reports. The average market grade of turkey broilers was improved by feeding dianisylhexene at 0.011 per cent of the ration and triphenylchloroethylene at 0.022 and 0.044 per cent for two and three weeks (146). Dianisylhexene fed to more nearly mature birds of both sexes also improved the fat grade (36). Levels between 0.009 and 0.018 per cent were equally effective, and the improvement was as great after two weeks of treatment as after four weeks. Triphenylchloroethylene (0.07 per cent) and triphenylbromoethylene (0.055 per cent) fed to 22- to 24-week-old turkeys of mixed sex and breed for 19 days during hot weather produced considerable improvement in the finish of the males but no improvement in the females (67).

Commercially Important Aspects of Estrogen Treatment

Effect on Carcass Quality. The primary object of estrogen treatment of poultry is improvement of carcass quality. Estrogen treatment has at least some influence on each of the components of carcass quality, and for the most part the influence is favorable.

Fatness is the best known advantage gained by estrogen treatment. Extra subcutaneous depot fat improves the finish of the dressed carcass. A doubling of the breast-muscle fat is frequently attained, and leg fat may be increased threefold or more with consequent improvement in the "juiciness" of the meat. A moderate amount of visceral fat is desirable for culinary purposes, but an excess is wasteful. Visceral fat may be increased manyfold (8, 15, 37, 52, 83, 90, 91, 92, 93, 94, 95, 126, 141, 151). Meat quality is also improved by a lightening of the flesh color and an increase in tenderness (93, 126, 133). These effects may be partly due to increased fat content, but the latter may also result from suppression of androgen and its toughening effect on the flesh (63). Flavor is more difficult to evaluate and measure objectively, and preference rat-

ings may not always distinguish flavor from texture and tenderness. Presently available reports (53, 68, 93, 137, 138, 140) are somewhat inconclusive and inconsistent, but the general market reaction indicates satisfactory consumer acceptance of treated birds. Stability of the meat in storage (of turkeys at least) is unaffected by estrogen treatment (132).

Finish is improved and a smooth "silky" texture is imparted to the dressed carcass by the increased subcutaneous fat and by the effects of estrogen on skin structure and on feather growth. Blemishes due to fighting are usually decreased, but in turkeys (and rarely also in chickens) scars due to attempted treading may be increased. Mixed flocks of treated males and females together are especially susceptible to damage from this cause. Estrogens increase skin tenderness (64), and extra care during scalding and plucking has sometimes been found necessary. The occasional need for extra care because of bone fragility has already been mentioned. Treated birds suffer less shrinkage than do untreated birds during live shipment and dressing (5, 112, 133), presumably at least partly because of decreased moisture content of the meat (37). Rendering of the excess fat results in increased loss during cooking (133).

The grade of the dressed carcass represents in some measure an attempt to synthesize all of the above characteristics into a single evaluation, but lack of uniformity of criteria and of scoring systems makes comparison of results difficult. Moderate to very striking improvements in grade have been reported for treated chickens (5, 8, 51, 52, 53, 113, 126, 137, 138, 141), and in turkeys the results have varied from no improvement to moderate improvement (6, 35, 36, 62, 67, 100, 125, 130, 135). The pale, shrunken combs and wattles are a complication to grading now well understood by the trade. This condition may be avoided by administering androgens (70), but the over-all consequences of such a combination treatment have not been adequately investigated.

The extent of these effects on carcass quality depends on the length of treatment, the estrogen used, its dosage and route of administration, and the age at which treatment is started. Broilers may easily be overfattened with diethylstilbestrol pellets for most present-day markets, especially if time is allowed for the full response to develop. Consequently, there has been a tendency to shorten the treatment period to four weeks or less. The age to start treatment has been considered to depend on desired market age and treatment period, but birds treated too young may sometimes react adversely. Six weeks of age is not too young for pellet implantations, but eight weeks has been suggested as the minimum desirable age for use of the more rapidly absorbed paste suspension.

In England, by contrast with the situation in the United States, interest appears to be centered in producing treated birds of the age and size of the usual surgical capons (21, 22, 23, 76, 77). Prolonged treatment periods have been used, even extending for several months and requiring reimplantation. Pellets of hexestrol have been reported to be especially suitable for this purpose. The advantage of such long treatment periods for carcass quality is uncertain. Adult cocks are well fattened during three to five weeks of estrogen treatment (93, 126, 137, 138). Mature female chickens have failed to respond (1, 137, 147), but the carcass quality of hen turkeys has been considerably improved by estrogen treatment at the close of the breeding season (111, 125, 135). Whether holding the birds the additional time necessary for treatment would be economical is questionable (135).

Growth and Feed Consumption. Increased feed intake during treatment has been almost uniformly observed (5, 8, 12, 15, 17, 23, 37, 51, 113, 144, 145), and at least a slight stimulation of total growth has been noted almost as frequently, although occasional slight depressions in rate of gain have been reported. The relative effect of estrogen treatment on gain in body weight increases with increasing

age of birds (5, 8, 12, 23, 37, 51, 52, 92, 93, 133, 137, 138). Estrogenic substances mixed in the feed in moderate dosages have had no effect, on the average, on rate of gain in growing birds. Individual instances showing slight depression have just about counterbalanced those where slightly greater gains were reported (15, 51, 92, 95, 144, 145). With dosages as high as 0.01 per cent, consistent slight additional gains were obtained by feeding dienestrol diacetate (95), but similar levels of dianisylhexene caused birds to go "off feed" and make unsatisfactory gains after the second week of treatment (75). Feeding estrogens to adult cocks has produced striking gains similar to those produced by pellets (126). The gross efficiency of feed conversion is usually (but not always) somewhat reduced in estrogen-treated birds (5, 8, 12, 15, 37, 51, 52, 113). When calculated as calories deposited per calorie consumed, the efficiency may be increased (8).

The growth and feed conversion results with turkeys have been less definite. Slight growth depression has been at least as common as slight growth stimulation (6, 35, 36, 67, 83, 91, 130, 146). Some growth stimulation was obtained during the second week, with loss of part or all of the advantage during the remainder of the treatment period (36, 146). In these trials feed efficiency was better in treated birds than in the controls when the growth rate was high; when it was low, efficiency was low also. Improved growth rate and feed efficiency were observed in small white turkey broilers treated with one diethylstilbestrol pellet (6). When two pellets were used, however, these effects were not obtained, an example of the sensitivity of this species to overdosage.

The mechanisms of these effects are undoubtedly complex. Stimulation of lipogenesis may exert either a positive or a negative effect on total growth, depending on whether fat is deposited in addition to, or in lieu of, other tissue. It will have a net negative effect on feed efficiency in either case, because of the higher caloric content of adipose tissue. The increased feed consumption, together with decreased energy expenditure due to the inhibition of aggressiveness, should favor accumulation of weight and higher feed efficiency but will be at least partly counterbalanced in turkeys by the stimulation of sexual activity. The possible relation of estrogen to the basal metabolic rate remains unproved, as mentioned previously. Stimulation of growth-hormone production or an androgen-like action of estrogens in promoting nitrogen retention are attractive hypotheses but also remain unproved.

Interactions of Estrogens with Ration Composition

The lipogenic action of estrogen is independent of the nutritional status of the bird (97, 153, 155), but the total amount of fat deposited is not. Kaffir, wheat, and corn have been reported to be superior to oats and barley for fattening in rations containing dianisylhexene (145). Diets containing 15 per cent and 18 per cent protein fed to 12-week-old cockerels produced an increase in fat deposition on the lower level of protein greater than that obtained by estrogen feeding (18). The birds on the high-protein diet gained more weight and had better food conversion than those on the low-protein ration but were "lean, blue, and lacking finish." Various "high-density" broiler mashes (52, 151) improved rate of gain, feed efficiency, and "finish" or grade of the dressed carcasses over that obtained on the standard mash. The average grades obtained on some of these high-density rations were as good as observed in birds treated with estrogens regardless of the ration used. The percentage of leg-muscle fat was always increased by diethylstilbestrol pellets, however. The effect of ration density on response of broilers (killed at 12 weeks) to different estrogen treatments has been studied by varying the amount of fibre in the ration (99). The low-fibre diet permitted the greatest responses to the various treatments, both in

regard to additional gains and to the amount of fattening. Feed efficiency was decreased, as compared to control birds, by all treatments on the high-fibre ration, but dienestrol diacetate actually improved feed conversion on the low-fibre diet. Pellets reduced it a little on all diets. Much work remains to be done on the interaction of estrogen treatment and diet.

Numerous experiments with estrogens combined with antithyroid drugs (8, 24, 37, 62, 83, 113, 122, 126, 134, 139), as discussed more fully in the succeeding section, have demonstrated that the combination prevents the growth-depressing effect of the latter. Lower dosages are reported to give more satisfactory results when both materials are used than when either is used alone (37).

Toxic Effects of Estrogen Treatment

Repeated implantations of diethylstilbestrol pellets have produced severe atheromatous lesions in cocks (28, 86), but such an arteriosclerosis has not been observed to affect the health of birds during the usual fattening period. Large doses of estradiol benzoate injected from an early age (153, 155) produced dwarf cocks. These birds eventually suffered fatty embolism of the lungs, followed by hemorrhage into the bronchi. The study suggests that the normal effects of estrogen treatment may be exaggerated into a disability. Dianisylhexene is the only estrogenic compound shown to have toxic effects during the usual fattening period (144). Deaths have occurred in a small to moderate percentage of birds treated with this compound; distended kidneys and small intestinal hemorrhages were noted at autopsy. The toxicity of other dimethylethers has not been determined. Estrogen-treated birds have been reported to go "off feed" and to make subnormal gains during hot weather (5) and also to react with more than usually severe symptoms to intercurrent disease. Commercial broiler growers have frequently reported excessively moist droppings from treated chickens, which are somewhat of a nuisance because of the resulting wet litter.

Hormone Residues in Treated Birds

Studies of the estrogen content of poultry flesh have been made in several laboratories. Dianisylhexene, dianisylhexane, and dianisylhexadiene were found in amounts of 2.5 to 4.3, 5, and 1.5 milligrams respectively per 100 grams adipose tissue in abdominal fat of birds fed these materials at the rate of 0.013 per cent of the diet for seven to twelve days (16). Other tissues contained smaller amounts roughly corresponding to their fat content. Similar estimates were obtained for dianisylhexene (98) when this material was fed at levels of 0.0033 to 0.025 per cent of the diet for three to six weeks.

Assays of tissues of birds fed dienestrol diacetate, based on vaginal cornification of spayed rats (16, 20, 57), have more commonly than not resulted in completely negative responses in the assay animals, with only a few positive responses reported from mixed muscle and skin extracts (57). Using uterine growth of weanling rats (a more sensitive procedure), a range of values of 0.003 to 0.01 milligrams per 100 grams of adipose tissue was obtained (98). The concentration in liver tissue was a little higher, but the average estimated amount of dienestrol diacetate in the entire edible carcass was less than 0.009 milligrams. These data include assays on tissues of birds fed this material for periods varying from twelve days to thirteen weeks and at feed levels varying from 0.0033 per cent to 0.013 per cent.

Injected diethylstilbestrol, whether in oil solution or in pellets, has led to estimates of tissue levels very similar to those found for dienestrol diacetate (16, 20, 57, 98, 129). Spayed rats have usually failed to respond to extracts of treated birds. Assays of pelleted chickens made with spayed mice (129) led to estimates of 0.13 $\pm$ 0.03 I.U. per gram of carcass and 0.24 $\pm$ 0.19 I.U. per gram of liver. These values correspond to an estimate

of 0.014 milligrams diethylstilbestrol (calculated from published estimates of relative potencies of various estrogens (16, 131)) in the entire edible carcass of a hypothetical one-kilogram bird with a 40-gram liver.

The most serious criticism of these data is based on lack of proof of the efficiency of the various extraction procedures used. Largely because of this criticism, an extensive assay program is now under way (139) using tissues of treated birds from various laboratories, including that of the author. An extraction procedure involving preliminary lyophilization, which accomplishes complete extraction within the experimental error of the determination (139) and the exceptionally accurate Curtis method for estrogen assay (34) is being used.

The significance to human health of tissue retention of estrogens has been examined (16). Menopausal women were fed diets containing either eight livers or 43 grams of rendered fat of treated birds daily for six days. Some vaginal cornification was obtained when tissues of dianisylhexene-treated birds were fed, but no demonstrable effect was produced by tissues of birds treated with dienestrol diacetate. Tissues of diethylstilbestrol-treated birds would probably have likewise produced no effect, since tissue retention of the last two compounds is similar. The effects, even with dianisylhexene, were mild and were produced by an abnormally high percentage of chicken products in the diet. Consequently, in all probability there is little or no danger to human health under normal conditions and usual dietary habits from the consumption of meat of estrogen-treated birds.

In one instance (129) normal beef liver was found to contain at least as much estrogenic activity as tissue from diethylstilbestrol-treated birds. Although this comparison is not entirely valid, because of the difference in nature and source of the estrogens involved, it does point up the relative insignificance of the tissue retention of this compound. On the other hand, the relatively higher tissue retention of dimethylethers of the stilbenes, and the demonstrated effect of one of these on vaginal cornification, make these compounds undesirable for fattening, at least until more extensive data are available.

An entirely different problem is posed by the unabsorbed portions of pellets that remain in the neck. Pellets should be implanted high in the neck, and these should normally be discarded with the head during preparation of the bird for consumption. However, an occasional pellet may remain on the carcass, especially if it is carelessly inserted or if it migrates downward after insertion. The danger of any noticeable effect due to accidental consumption of such residue appears to be remote. The probability of any one person consuming a residue repeatedly is very low, and estrogens normally manifest their effects only after a period of repeated or continuous administration. However, poultry offal from treated birds is unsuitable for feeding to other animals because of these residues. Unabsorbed residues of orally administered estrogens in the intestinal contents may pose a similar problem to use of offal if feeding estrogens becomes a practice.

Evidence of estrogen in eggs of treated birds has been adduced by the observation (2, 4) that chicks hatched from eggs of treated birds exhibited reproductive abnormalities. This observation should suggest caution in the use of any chronic estrogen treatment for interruption of broodiness. An acute treatment, such as a single injection of an oil solution (55), should be less liable to result in egg deposition, but investigation of this procedure by assay of the eggs would be desirable.

Restriction on Use of Estrogen for Fattening

Estrogen treatment of poultry has not been permitted in Canada (59), but diethylstilbestrol is available in the United States for this purpose. Estrogen preparations intended for fattening poultry are considered new drugs. Several new drug applications have

become effective for pellets containing 12 to 15 milligrams of diethylstilbestrol and one for a paste suspension containing 15 milligrams of diethylstilbestrol per dose. No applications for estrogen preparations intended for oral administration to poultry have become effective and, to the best of the author's knowledge, none have been made at this writing.

An important consideration, apparently, in those new product applications that have become effective (30) is labeling with instructions for implantation high up on the neck as near to the head as possible. The purpose of these instructions is, of course, to minimize the possibility that the unabsorbed residue might be ingested by the consumer, by placing it in a portion of the bird not ordinarily eaten (93). Recently dressed poultry in considerable numbers were seized because the pellet residues were found in edible portions of the bird. Most of the birds examined from the seized lots had pellet residues an inch or more below the base of the skull. Most of these improperly located pellets probably resulted from careless implantations, but the possibility exists that even properly implanted pellets may migrate downward into the edible neck region.

Summary and Recommendations

Estrogen treatment is a useful commercial procedure and can be recommended for improving finish and quality in all classes of meat chickens except mature hens. Slight increases in rate of gain may also be obtained in chickens with estrogen treatment. This is accompanied by increase in feed consumption, and the gross feed efficiency is usually slightly reduced. The improvement in carcass quality usually more than compensates for increased production costs.

Estrogen treatment for turkeys is less certainly useful than for chickens. It is probably most advantageous for finishing immature birds but must be used with caution. Overtreatment must be avoided and careful management is necessary to minimize undesirable side effects.

Turkeys fatten less dramatically than do chickens in response to estrogens, but other effects, such as feathering, are improved as much or more. Estrogens have been reported to stimulate growth and improve feed efficiency; whether failure to obtain these effects uniformly is due to suboptimal conditions or to undesirable side effects is not known.

Estrogens used for treatment should be limited to those compounds, such as diethylstilbestrol and dienestrol diacetate, that are retained in negligible quantities in poultry flesh. Where pellet implantation is the method employed, care is necessary to avoid the presence of unabsorbed residues in edible portions of the carcass. Offal from estrogen-treated birds should not be used for animal feed.

Estrogen treatment for interrupting broodiness should be considered an experimental method only, at least until more information is available on estrogen deposition in eggs.

More investigational work is desirable on numerous problems, especially:

1. Determination of relative estrogenic potencies for birds and tissue retention of several compounds that have shown promise.

2. More exact determination of optimum dosages and treatment periods, for chickens and particularly for turkeys.

3. More studies of interactions with ration composition and with antithyroid drugs, with emphasis on determination of minimum estrogen treatment for optimum results.

4. Further studies on factors influencing absorption of parenterally administered estrogens, with emphasis on reducing or eliminating unabsorbed residues.

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THYROPROTEIN AND ANTITHYROID DRUGS IN POULTRY FEEDING

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The ready availability of synthetic thyroprotein preparations (85) and goitrogenic compounds (9) has stimulated interest in recent years in the possibility of regulating the level of thyroid hormone for productive purposes. Knowledge of the physiology of the thyroid, necessary for the intelligent application of these drugs, has accumulated over a period of many years, with modifications introduced by recently developed techniques of study.

The thyroid has long been known to be concerned with regulation of metabolic rate. In mature chickens basal metabolic rate decreases with age (34), is higher during periods of active egg production than in nonproductive periods (34), and exhibits a seasonal rhythm correlated with egg production rate (133, 134).

In addition to reduced metabolic rate, the consequences of removal or destruction of the thyroid include slow and abnormal growth and feathering in young chickens (135, 136), and in mature birds greatly decreased egg production (103, 132), reduced egg size and thinner egg shells (103), slow feathering and changes in feather types (21). These effects can be largely, if not completely, reversed by the administration of thyroid hormone.

In excessive amounts, i.e. in amounts such that the level actively present in the body exceeds the normal output of the thyroid gland, thyroid hormone administration has the following consequences in mature birds, depending on the level given: increased metabolic rate; weight losses, with males more sensitive than females (59); more rapid molting and feather growth (26); reduction in egg yolk size (6, 7); increase in proportion of egg shell (7); cessation of egg production (8); and death (59). Feeding sources of thyroid hormone to growing rats, mice, dogs, or chickens increases their requirements for certain vitamins (33). In the case of the chick, enhanced requirements for vitamin B_{12} (81, 88), vitamin E (127), and vitamin A (27) have been shown; indications of involvement of vitamin D (74), pantothenic acid (52, 79), and folic acid (52) have also been reported. These can be considered to be thyrotoxic effects. Work with rats has shown that thiamine (31, 32, 101), vitamin A (71), niacin (63), pyridoxine and pantothenic acid (31), vitamin B_{12} (15, 35, 102), fat (46), methyl linoleate (47), and lyxoflavin (36) are "antithyrotoxic" factors. At least one unidentified nutrient in liver (15, 38, 39, 40) is also concerned in overcoming the effects of high thyroid hormone level in rats and mice. Antibiotics also appear to have an antithyrotoxic effect (75).

THYROPROTEIN

Regulation of the active level of thyroid hormone in the body is a function of the anterior pituitary through its thyrotrophic hormone. Output of the thyrotrophic hormone is inversely related to the level of circulating thyroid hormone, and the output of the thyroid gland is a direct function of its stimulation by the thyrotrophic hormone. Normally, a state of dynamic equilibrium exists. If exogenous thyroid hormone is introduced into the system, the output of the thyroid gland diminishes accordingly, ceasing entirely when its normal output is equalled by the outside supply. When the exogenous supply exceeds the normal output, the animal becomes hyperthyroid. The theoretical basis for improving productive performance of chickens by administration of thyroprotein, therefore, is the achievement of a controlled hyperthyroid state in those circumstances where the consequences of hyperthyroidism and increased metabolic rate are desirable.

Basic to the application of synthetic thyroproteins to poultry production is a clear understanding of the magnitude and significance of normal thyroid secretion rate of birds in various states of growth and production. The method of Dempsey and Astwood (29) for determining thyroxine secretion rate has been adapted for use with poultry (76) and applied by several groups of investigators. The results of these studies can be summarized as follows:

1. Species differences between ducks, turkeys, and chicks suggest that thyroxine secretion rate is related directly to rate of growth (16, 20, 56. 76, 98).

2. Thyroxine secretion rate per unit of weight declines with age of growing birds (16, 76).

3. Rapidly growing strains of chicks show a higher thyroxine secretion rate than slowly growing strains within the same breed (44), and so-called hybrid chicks (incrossbred) show a higher secretion rate than chicks of the parent lines (78). However, no differences were found between fast- and slow-feathering strains of Rhode Island Red chicks (24).

4. Young chicks show a direct relation between thyroid secretion rate and light exposure (65).

5. In 10-week-old chicks, thyroxine secretion rate was found to be inversely related to temperature and directly related to size of the thyroid gland (57).

6. A seasonal trend in the thyroxine secretion rate of 2-week-old chicks from a high point in the fall to a low in the early spring has been observed (86).

7. Thyroxine secretion rate of hens is low. An attempt to determine its seasonal trend showed a tendency toward decline from winter to spring, but the data were insufficient to show whether the trend continued into the summer (116).

8. Hens laying in 4-egg cycles show a somewhat higher thyroxine secretion rate than similar hens laying in 2-egg cycles (23).

Whether the thyroxine secretion rate is a cause or an effect of the productive characteristics to which it appears to be related has not been demonstrated. The fragmentary evidence cited above and the functions of the thyroid previously discussed can only suggest that there may be practical value in a controlled hyperthyroid state. The following sections summarize the available information on the feeding of synthetic thyroprotein preparations.

Effect on Egg Production

A series of reports by Turner and associates (109, 110, 113, 114, 118, 120) describes studies with small groups of hens in successive production years. Preliminary work indicated that levels of 35 grams or more of Protamone (iodinated casein estimated to contain 3 per cent thyroxine*) per 100 pounds of feed caused weight losses and cessation of egg production. Further work indicated that apparently optimal results were obtained by feeding 10 grams per 100 pounds of total feed intake, and this level has been generally used by this group and others in subsequent studies. The reports by Turner and his associates showed improved annual egg production through seven successive production years by feeding Protamone, with little effect on body weight or egg size. In these experiments, the hens were confined to individual cages, and in no case did the experimental groups in any year contain more than 21 surviving hens; as few as three hens constituted a group in one case. In an experiment unrelated to this series, higher egg production was obtained during the pullet year from birds fed Protamone at 10 grams per 100 pounds than from similar pullets fed the stock ration (119). The workers have interpreted their results to show 1) that the normal seasonal decline in egg production during the latter part of the production year is due to lowered thyroxine secretion and is

* More recent work indicates that the thyroxine content of this product is more probably 0.3 to 0.7 per cent.

overcome by thyroprotein feeding, and 2) that thyroxine secretion decreases with age year by year and the deficiency is supplied by thyroprotein with consequent improvement in egg production. These hypotheses have been based largely on seasonal variations in thyroid size (large in winter and small in summer (42)) and similar seasonal changes in iodine content (28), with the assumption that they reflect directly the rate of thyroid hormone secretion. Neither hypothesis has been substantiated by direct determination of thyroxine secretion rate.

Other groups of investigators have been unable to confirm the results of Turner and associates (14, 45, 49, 50, 55, 60, 69, 70, 104, 131). These studies have included tests at the end of the production year for relatively short periods to study the period of seasonal decline (45, 49, 56), as well as longer trials with substantial numbers of birds (50, 60, 70, 104). In one investigation (131) Protamone was studied in relation to the effects of controlled high temperatures on laying hens and showed no effect on egg production. Intensive egg production trials in laying cages (14, 69) have shown no beneficial effect from Protamone. In three studies (14, 55, 60), feeding Protamone at a level of 10 grams per 100 pounds of feed intake reduced egg production.

Two recent studies have been conducted to investigate some of the possible reasons for the disagreement between Turner's group and the others who have worked in this field. In the most recently reported study of Turner and associates (91), the effect of Protamone on egg production of pullets in individual cages was studied in relation to the supplementation of the ration with animal proteins and B-vitamins, including vitamin B_{12}. No differences in egg production rate were produced by Protamone regardless of the kind of ration employed, in contrast to the previous results reported from this laboratory. The other recently completed work (70) investigated the effects of vitamin B_{12} and energy level on the response to Protamone in experiments over a period of two years. No stimulation of egg production was produced with any of the rations employed.

Effect on Egg Quality

Egg Size. A decrease in egg weight, due to Protamone and significant in two of three trials, has been reported in studies concerned with the effects of controlled high temperatures on production (131). Other investigators (14, 45, 55, 60, 69) report no significant difference due to Protamone feeding, in agreement with the studies of Turner and associates (cited above).

Shell Thickness. Shell thickness, as measured by specific gravity of the egg by 14-day incubation weight loss or by direct measurement, was significantly improved in five studies (14, 45, 49, 55, 90, 131). No difference was found in these measurements or in breaking strength in two other studies (45, 60). The magnitude of the difference as measured by specific gravity was relatively small in relation to the seasonal decline which normally occurs from winter to summer (55). In one study specifically designed to investigate shell quality, shell thickness was improved most in birds showing initially thin shells; it was suggested that shell improvement might have been a consequence of decreased rate of production (14).

Other Criteria. Shell smoothness and albumen index have been reported to be unaffected by feeding thyroprotein (14).

Weight Maintenance in Mature Chickens

The series of studies by Turner and associates showed no consistent effect of feeding Protamone at the rate of 10 grams per 100 pounds of feed on maintenance of weight in hens. Similar results have been obtained by others (45, 60, 69, 131), but in two cases significant weight losses at this feeding level have been reported (14, 55). Mature males have been shown to lose weight at this feeding level (96). Apparently Protamone at 10 grams per 100

pounds of feed intake is near the limit of tolerance for females. At this level of feeding, decrease in thyroid weight has been the only consistent change in organ size (113, 117).

Effect on Hatchability and Embryonic Development

Protamone fed at 10 grams per 100 pounds of feed had no effect on hatchability (45, 50, 73, 123). Incubation time required for normal hatching was significantly lengthened, however, and the chicks produced showed enlarged thyroid glands (125, 126). The degree of enlargement was proportional to the level of Protamone fed (126).

The mechanism through which feeding Protamone to hens results in enlarged thyroid glands in their newly hatched chicks is not clear. Feeding Protamone to hens did not produce a detectable amount of thyroxine in the egg, according to guinea pig assay (109), and the injection of thyroxine into hens had no effect on the thyroid weights of their chicks (72). It would be logical to expect that any thyroxine deposited in the egg would result in a decreased chick thyroid weight as shown experimentally when thyroxine and Protamone were injected into the incubating egg (22); however, another study in which small amounts of thyroxine were injected into eggs during incubation showed increased thyroid weights of newly hatched chicks, indicating a possibility that this phenomenon may be related to the size of dose (90). Estimation of metabolic rate of chicks from Protamone-fed hens by a closed vessel survival technique indicated that the chicks were hypothyroid, although the data are neither extensive nor clear cut. The inorganic iodide contained in Protamone has been implicated in this goitrogenic effect, and it has been clearly shown that the amount of iodide contained in Protamone is sufficient to explain its goitrogenic action (128, 129). However, a sample of Protamone, prepared in such a way that it was free of inorganic iodide, still showed the goitrogenic effect in newly hatched chicks (130). It is possible that iodide produced *in vivo* from the diiodotyrosine known to be present in Protamone was responsible for the effect, or that some more obscure mechanism is concerned. Thiouracil fed to breeding hens has a similar goitrogenic action on their progeny because of transfer of thiouracil into the egg (3).

Effect on Growth, Feathering, and Development

The normal rate of thyroxine secretion in chicks is approximately equalled by feeding 4 grams of Protamone per 100 pounds of feed (93); 33 milligrams of crystalline DL-thyroxine, or half this amount of its sodium salts, per 100 pounds of feed is similarly effective (79). In 2-week-old chicks, feeding 5 grams or more Protamone per 100 pounds of feed increased metabolic rate; for older chicks up to 8 weeks of age, 10 grams or more was required to raise metabolic rate (97). In these studies, mortality occurred when chicks fed the higher levels of Protamone were fasted.

An early experiment (82) on the effect of thyroprotein on chicks showed significant growth stimulation through 12 weeks of age by feeding .025 per cent, with an accompanying improvement in feed efficiency. Feathering was markedly improved by higher feeding levels (0.1 to 0.2 per cent) only. It appears probable that this material had lower thyroid hormone potency than samples used later by other investigators, but the study is of particular interest because it showed that higher levels are required for feathering improvement than for growth stimulation.

Using Protamone represented to contain approximately 3 per cent thyroxine,* the limit of tolerance for chicks up to 12 weeks has been shown to be approximately 50 grams per 100 pounds of feed (24, 61). Above this level growth was depressed, although feather development was improved even at much higher levels.

* More recent work indicates that the thyroxine content of this product is more probably 0.3 to 0.7 per cent.

Feeding up to 36 grams per 100 pounds of feed, with 10 grams the level most commonly employed, has shown highly variable results. Early growth stimulation, up to 6 weeks of age with the advantage lost by 12 weeks of age, was reported in early studies (61). Similar early stimulation, with male chicks significantly heavier and more uniform at 12 weeks, was obtained by others (121). No significant improvement was obtained by other investigators (1, 24, 67, 108). Part of the disagreement between experiments may be explained by strain differences in response (44) which appear unrelated to rate of growth. Another possible reason for inconsistent results is the influence of Protamone at 10 to 15 grams per 100 pounds of feed in increasing vitamin requirements, such as for vitamin B_{12} (88).

The most consistent effect of Protamone during early growth is to improve feather development (24, 44, 61, 82, 108, 121). This effect is not related to growth stimulation (24, 44, 61, 108) but is roughly proportional to the level of Protamone fed even in the dosage range which retards growth (24, 61). The response depends on the strain of chicks, with rapid-feathering strains showing no effect (44), and is most marked up to 8 weeks of age.

Only one report (122) is available on the effects of feeding Protamone throughout the growing period. In this study growth was improved in both sexes at 6 weeks, was superior only in males at 12 weeks, and was unaffected in the period from 12 to 24 weeks. Sexual maturity was significantly delayed in females fed Protamone.

Thyroid weights have been lowered consistently by feeding Protamone to growing chickens. Effects on other organs have not been consistent. In one study covering the entire growth period, comb and testes weights were depressed in early growth and testes weights greatly increased in the latter part of the growth period (121, 122). Still later when the cockerels had matured, testes weights were lower than normal and volume of semen production was depressed, although fertility on a flock mating basis was apparently normal (58). Little if any effect on testes weight was reported in another study (67) and reference was made therein to work indicating that the effect of Protamone on testes development varied widely within a relatively narrow dosage range. Semen quality and fertility were reported to be adversely affected in mature males (96). No effect of feeding thyroxine on fertility of older males in natural matings was noted (53).

Investigation of the nature of growth stimulation by thyroxine in mice (66) has shown that less fat deposition occurs in treated mice, with a resultant decrease in efficiency of use of feed energy. A somewhat similar study with growing chicks, using Protamone, has been reported (1) in which individually fed chicks were used under conditions of controlled feed intake. In this work, no difference in growth was observed but the Protamone-fed birds showed somewhat lower fat deposition. Indication of low fat content in Protamone-fed chicks has also been reported by others (108). Gross efficiency of feed utilization has been improved by Protamone only when significant growth stimulation has also been obtained (61, 82, 84, 121), although not invariably so (44).

Growth of worm-infested chicks was improved by feeding 0.04 per cent Protamone, but not to the extent of equalling the performance of normal controls (106). On the other hand, feeding 0.02 per cent or 0.04 per cent Protamone had no effect on growth or survival of chicks exposed to experimental coccidiosis infection (107, 124).

Recommendations

Mature Birds. The weight of evidence shows that feeding thyroprotein to laying hens has no stimulatory effect on egg production. The contrary results of the Missouri studies may be fortuitous because of the small number of birds employed, or may be indicative of unique experimental conditions. The extent of the improvement in egg shell quality which thyropro-

tein produces appears hardly sufficient to justify its use. Its deleterious effects on semen quality, fertility, and weight maintenance in breeding cockerels, together with its goitrogenic effect on the incubating embryo, argue against its use in rations for breeding flocks.

Growing Birds. The effect of thyroprotein on early growth rate is inconsistent, apparently due at least in part to strain differences in the responsiveness of chicks. Because of this, its general use cannot be recommended. It should not be used during the latter part of the growth period because of its deleterious effect on sexual maturity of pullets and reproductive activity of cockerels.

Although the most consistent effect of thyroprotein in early growth is to improve feathering, it has very limited usefulness for this purpose because 1) the effect is usually pronounced only in early life, up to 8 weeks of age, and 2) the levels required for significant improvement at the usual marketing time of young meat birds are in the growth depressive range.

The use of thyroprotein in feeds for poultry is permissible in the United States, although no extensive commercial use of this product is known to the author.

ANTITHYROID DRUGS

Basic studies of synthetic goitrogenic compounds (9) and demonstration of their activity for chicks (10) have been followed by many studies of their possible application in fattening meat poultry.

The underlying mechanism of action of synthetic goitrogens of the thioureylene type is interference with the synthesis of thyroid hormone within the body rather than interference with the action of the hormone. The effects of the drug on the animal are, therefore, essentially similar to partial or complete thyroidectomy. Metabolic rate is lowered (29, 97) and a greater proportion of feed energy is deposited as fat (25). Probably because of impaired ability to regulate body temperature, thiouracil-fed rats show low resistance to the stress of low environmental temperature (37). An indication that thiouracil-fed chickens may be less disease-resistant has been reported (95), but this was not evident in experimental coccidiosis (124). Evidence has been obtained indicating that the effects of the thiouracil feeding in rats may extend beyond interference with thyroid hormone synthesis, because the thyroidectomized rat is much more sensitive to small doses of thyroxine than is the thiouracil rat (12). Such effects, if characteristic also of poultry, would probably limit the dosage and time of treatment in the use of goitrogens.

Most of the research with poultry has dealt with the use of thiouracil because it is one of the most active goitrogens for chickens (10). Thiourea appears to be at least equally active for producing thyroid hypertrophy, but is more toxic than thiouracil for chickens (93). Thiobarbital has about twice the goitrogenicity of thiouracil for chicks (112), and propylthiouracil shows a marked fattening action at low levels (62); further data are needed before practical application of either of these compounds can be made.

Effect of Thiouracil on Growth and Carcass Quality

Maximum enlargement of the thyroid gland in young chicks has been obtained by feeding 0.1 per cent thiouracil in the diet (76, 93). Feeding this level from hatching time continuously up to 10 weeks of age did not impair growth as measured by body weight in two studies (10, 67), but did depress both growth and efficiency of feed utilization in others (43, 112). Higher levels depressed growth at an earlier point (67).

In later stages of growth, less growth depression has been obtained in chickens from thiouracil feeding. When treatment with 0.2 per cent thiouracil in the diet was started at 6 to 12 weeks of age, little or no effect on growth was observed for feeding periods from 2 to 4 weeks (30, 51, 64, 80). Longer feeding periods,

5 to 8 weeks, affected growth adversely (4, 5, 30, 64). Older birds showed no adverse effects during periods up to 4 weeks of feeding (77, 92) and in one study growth stimulation was noted in feeding the 0.1 per cent level to 16-week-old birds (77). Gross efficiency of food utilization was either unaffected or somewhat lowered with the single exception of the study in which growth stimulation was observed. Improved carcass quality was observed in all cases in which 0.1 per cent or more thiouracil was fed, except for one case in which 18-month-old males were treated for a 3-week period. Carcass fat determinations showed the stimulating effect of thiouracil on fat deposition (5, 30) and showed that the efficiency of gains was improved on an energy basis by thiouracil.

Studies with turkeys have generally, but not invariably (89), shown depressed growth during treatment with 0.1 per cent or 0.2 per cent thiouracil for periods of 3 to 4 weeks (19, 100). The effect on efficiency of feed utilization has not been consistent. Carcass quality has shown improvement by thiouracil except under conditions such that excellent quality was also shown by the control birds (87).

Thiouracil-Estrogen Combinations

A synergistic relation of thiouracil and diethylstilbestrol (or its derivatives) in goitrogenic action (93, 94, 105) has led to investigation of the efficiency of combination treatments to overcome the disadvantages of growth depression frequently noted with thiouracil. Most investigations with chickens have been conducted up to 12 weeks of age, with treatment periods ranging from 3 to 6 weeks (5, 30). In these studies, carcass fat level and carcass quality have been greatest with feeding 0.15 per cent to 0.2 per cent thiouracil in combination with implantation of a 12- to 15-milligram pellet of diethylstilbestrol. Use of the estrogen largely, if not completely, reversed the depressive effect of thiouracil on growth and feed efficiency. In the case of 18-month-old cockerels, administering thiouracil at a 0.2 per cent level in combination with diethylstilbestrol was no better than the estrogen alone.

Results with turkeys have been similar, showing that a ration containing 0.2 per cent thiouracil used in combination with diethylstilbestrol implantation produced superior carcass quality without the growth depression exhibited by thiouracil when used alone (54, 68, 100). The combination treatment has not invariably produced superior carcass quality as compared with the estrogen alone, however (89). Of practical importance in turkey production is the possibility of advancing the marketing time of turkeys by producing satisfactory feathering and fleshing through treatment with this combination of hormones at an earlier age than usual. This would increase the efficiency of turkey meat production in relation to feed requirement per pound of meat produced, and would also serve to reduce the economic risks concerned by shortening the production period. It has been found possible to produce satisfactory market qualities in turkeys 17 and 21 weeks of age by subjecting them to implantation of 12, 24, or 36 milligrams of diethylstilbestrol and feeding a ration containing 0.2 per cent thiouracil for the preceding 4 weeks (100). The improvement was greater for males than females, and greater for turkeys marketed at 17 weeks than at 21 weeks of age. In general, the combination of thiouracil and estrogen was superior to the estrogen alone in enhancing carcass quality, and the 12-milligram level of diethylstilbestrol was as effective as the higher levels in most cases. Treatment initiated at 7 weeks of age for the purpose of marketing at 11 weeks was not successful, mainly because of the marked growth depression caused by thiouracil and the inability of estrogen to overcome it. It was noted that the incidence of torn backs, commonly produced by the increased sexual activity promoted by estrogen treatment, was less with the thiouracil-estrogen combination than with the estrogen alone. On the other hand, mortality was considerably higher in turkeys treated with

the combination of drugs. An economic analysis of the benefits of the thiouracil-estrogen treatment for turkeys has been made (2), indicating its value to the turkey producer.

Thiouracil-Thyroprotein Combinations

The growth depression characteristic of thiouracil feeding can be overcome by simultaneous feeding of a very low level of thyroprotein without losing much of the superior carcass quality (80). In chickens 12 weeks old, treatment with 0.2 per cent thiouracil for 4 to 5 weeks produced a growth retardation which was overcome by simultaneously feeding 1 gram of Protamone per 100 pounds of feed. This combination also produced greater thyroid hypertrophy than thiouracil alone. The carcass quality of the birds treated with this combination was invariably superior to the controls receiving no treatment, and was usually equal to birds fed thiouracil alone. It is of interest to note that the metabolic rate as measured by oxygen consumption of thiouracil-fed birds was returned to normal by feeding 1 gram of Protamone per 100 pounds of feed (97).

Persistence of Thiouracil in Tissues of Treated Birds

Three groups of investigators have studied this aspect of the use of thiouracil and are in general agreement that the level in tissues of treated birds is low (41, 68, 83). Studies of the metabolism of thiouracil in the chicken have shown that the blood level varies with the dietary level, frequency of feeding, and length of fast. It has completely disappeared from the blood within 24 hours of fasting, even when the feeding level has been as high as 0.6 per cent. Rat assay of the edible tissues of chicks 6 weeks of age fed levels of thiouracil up to 1 per cent of the diet for 1 week show a slight goitrogenic action equivalent to less than 5 milligrams thiouracil per 100 grams of chick tissue (83). In this assay the chicks were not fasted before being killed.

The dried tissues of 3-week-old chicks fed 0.2 per cent thiouracil showed goitrogenic activity equivalent to 3 $\pm$ 2 milligrams thiouracil per 100 grams when the chicks were killed without fasting. If fasted 24 or 48 hours, the tissue thiouracil fell to 0.1 to 0.05 milligrams per 100 grams (44).

Recent work with turkeys shows no evidence of goitrogenicity in tissues of birds fed 0.2 per cent thiouracil. Details of the work have not been published (68).

Cooking has no effect on the thiouracil in poultry meat, but storage at 4°C. for 1 week resulted in disappearance of most of the activity (41). The use of thiouracil alone or in combination with diethylstilbestrol for fattening turkeys has been shown to have no effect on the storage quality of the meat (99).

Natural Goitrogens

The distribution of natural goitrogenic activity in foods has been studied by Astwood and coworkers (48) and recently a pure goitrogen, L-5-vinyl-2-thiooxazolidone, has been isolated from yellow turnip by them (11). The only material used in poultry rations which has marked natural goitrogenic activity is rapeseed meal. Its effect on growth and thyroid hypertrophy has been studied with chicks (111, 115), showing that the goitrogenic activity is in the non-oil portion and that even at a high feeding level (40 per cent) it has less activity than 0.1 per cent thiouracil. In regions where rapeseed meal is a readily available feedstuff, its usefulness may be increased by feeding it in combination with Protamone (17, 18) or inorganic iodide (2) in order to counteract its growth depressing effect.

Recommendations

The use of thiouracil as a fattening and carcass-improving agent should be limited to relatively young meat birds and to a short period of time, probably not exceeding 4 weeks. It is ineffective in treating older chickens, such as 18-month-old breeding males.

Whether the more active goitrogens, thiobarbital and propylthiouracil, will prove to be more effective awaits further investigation.

The usefulness of thiouracil alone appears very limited because of its growth depressing effects. The evidence clearly seems to show that the use of thiouracil in combination with implanted diethylstilbestrol is an effective means of overcoming this growth depressing effect and produces market quality generally superior to that produced by either drug alone. Such a combination appears to have practical value in turkey production. The level of thiouracil needed is not in excess of 0.2 per cent of the ration. More data are needed to show whether a lower level can be used effectively.

The use of thiouracil in combination with thyroprotein also appears to be an effective means of overcoming the growth depression characteristic of thiouracil. Further data on this method of treatment and a possible triple combination with diethylstilbestrol would be useful in arriving at a more definite recommendation.

Danger to human health from residual thiouracil in tissues of treated birds appears remote from consideration of tissue levels in relation to effective doses for humans. Any hazard could be minimized either by withdrawing the drug for a few days prior to slaughter or by fasting the birds.

It is permissible to use thiouracil in poultry feeds in the United States. Application for the use of other goitrogens has not been made to date. Goitrogens have not been used commercially up to the present.

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SOME USES OF DRUGS AND HORMONES IN BEEF CATTLE, SHEEP, AND SWINE HUSBANDRY

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Ablation of the thyroid followed by replacement therapy was performed nearly 70 years ago by Schiff (64). However, only after Gley (34) called attention to the parathyroid as a distinct entity did a clear picture of the function of the thyroid gland emerge. That growth of young animals is greatly depressed following thyroidectomy has been demonstrated in several species of farm animals including sheep (41, 42, 66, 67, 68, 69, 76, 77), goats (61, 63, 69), swine (65, 84), and cattle (24, 71). Normal growth of young, thyroidectomized animals is fully restored by thyroid replacement therapy administered as injected or ingested thyroxine or as ingested thyroprotein (24, 63, 71). It has been reported that the fattening of pigs (90) and of growing beef steers (10, 25) has been accelerated by *partial* thyroidectomy.

It has been known for many years that changes in rate and type of growth take place at sexual maturity and that castration of males or females influences skeletal and muscular development, growth rate, fat deposition, and various metabolic processes. Castrates are preferred to normal males for meat production because of the more placid temperament of the former and their greater tendency to accumulate fat. Normal males, however, ordinarily grow more rapidly than do castrate animals, especially in early life. These changes at maturity and following castration appear to be related directly to the secretion of the sex hormones. A comprehensive discussion of the relationships between sex hormones and growth of animals has been given by Brody (24).

The foregoing observations have suggested that thyroprotein, the antithyroid drugs, and the sex hormones may be used to accelerate growth and to increase efficiency of fattening animals.

Effects of Thyroprotein on Swine and Ruminants

Increased efficiency in the utilization of feed and accelerated growth rates appear to have resulted from the feeding of iodinated protein to 40-pound weanling pigs at levels of 0.006 to 0.018 per cent of the ration, through feeding periods of 84 to 119 days (15, 16, 52, 53, 54, 62, 82). Reineke and McMillan (61) reported a significant increase in rate of gain and a slight increase in efficiency of feed utilization when thyroprotein was fed as 0.005 and 0.0075 per cent of the ration for only 56 days. However, less favorable results have been reported by some other workers. Vander Noot and coworkers (79) fed the drug through a 63-day period at levels of 0.075 through 0.225 gram per 100 pounds body weight to pigs that weighed between 40 and 50 pounds, with little or no effect. Unfavorable results were obtained when 0.5 to 4 grams per 100 pounds body weight were given through a period of 64 days, or when the drug was fed as 0.1 per cent of the ration through a period of 87 days. Braude (21) fed iodinated casein to growing pigs in daily doses of 1.5 grams or less, per animal, without significant acceleration of growth rates. Unfavorable results were reported by Muhrer et al. (45) when iodinated protein was fed, not to young growing animals, but to fattening pigs. Norfeldt and Hyden (48) found that growth rates and feed efficiency of pigs of about 100 pounds body weight were decreased by 0.46 and 0.91 gram iodinated casein daily per 100 pounds body weight when feed intake was limited to that of controls, but later, with ad lib. feeding, growth rates and feed efficiency of pigs given the thyroidal agent were superior to those of the controls.

The variability in these results probably is due to several factors. The effects of thyropro-

tein administration on swine may vary with environmental conditions, breed or even strain within a breed, and dosage at various stages of growth. Unfortunately, little information is given in the various reports concerning environmental conditions during the trials. Environmental temperature could well have been one of the important factors, if not the decisive one, in determining the outcome of any given trial. This opinion is supported somewhat by the experience of Beeson et al. (15) who reported that pigs given thyroprotein as 0.0088 per cent of the ration grew, in their earlier trial, 12 per cent (significant) and, in their later trial, 4 per cent more rapidly than the controls during winter trials, but this same dose administered during a summer trial resulted in only a 2 per cent increase in gain. That genetic factors may also play a part in the response of swine to thyroprotein was demonstrated by Reineke et al. (62) who found that an inbred strain of Chester White pigs responded unfavorably to a thyroprotein dose that had increased rate of gain and efficiency of feed utilization of Berkshire, Yorkshire, and Duroc Jersey pigs.

The part played by the level of thyroprotein dosage in changes in body size of the animal is undoubtedly of great importance. Perry et al. (55) found that growth rates of swine increased when the level of thyroprotein administration decreased per unit of body weight as the animals grew, but not when the dosage level remained stationary. This adjustment of dose to body size is accomplished automatically when thyroprotein is administered as a fixed percentage of a complete mixed ration, but does not necessarily take place when thyroprotein is added to a protein supplement. Maladjustment of the dosage to body size may be the explanation of some unfavorable results obtained by Perry and coworkers (55) when thyroprotein was administered to hogs on pasture at levels of 0.363 to 0.644 gram per 100 pounds body weight. Under these conditions, thyroprotein administration not only failed to increase rate of gain, but in the case of the highest level of administration it was accompanied by a significant depression of the growth rate. However, since these pasture trials were carried out during the summer, environmental temperature may have been a factor. The unfavorable results observed by Braude (21) when a stationary level of iodinated protein was administered to growing pigs, and by Vander Noot et al. (79) when dosage was based on body size rather than on feed intake, may have been due to the methods used by these workers in calculating their dosage levels of the thyroidal agent. The favorable responses obtained when iodinated protein was fed as 0.006 to 0.018 per cent of the ration to weanling pigs of about 40 pounds body weight, through periods of 84 to 119 days, offer a starting point for further research. Doubtless such additional research will outline more clearly the conditions under which increased production may be obtained with thyroidal agents, but at the present time the conditions under which favorable results may be expected to follow the feeding of iodinated protein are not well defined.

Results of the limited number of experiments in which iodinated protein was fed to ruminants are even less favorable than those in which the drug was fed to swine. Dinusson and associates (27, 28) reported that a daily dose of 0.5 gram thyroprotein per 100 pounds body weight decreased the rate of gain and efficiency of feed utilization of 500-pound beef heifers. These results are similar to those of Millen et al. (43) with dairy calves fed 1.33 grams of iodocasein daily per 100 pounds body weight. These workers also reported that calves given 4 grams of the drug daily per 100 pounds body size continuously lost weight.

Lambs that weighed, initially, 75 pounds, given daily doses of 0.5 and 1 gram of iodocasein for 42, 84, and 126 days, did not respond favorably (13). Upon autopsy, the thyroids of these lambs were found to be in a resting state (11).

The feeding of iodinated protein to rams was followed by inferior breeding performance and, in some cases, loss of weight (18, 30, 83). Bogart and Mayer (19), however, have indicated that hyperthyroidism in normal rams increased sperm production and decreased the percentage of abnormal forms during the summer months. In bulls, thyroidectomy results in decreased libido and interest in the estrual female (56), but these are restored by administration of thyroid according to Reineke (59) who fed thyroprotein to 14 aged bulls and noted an increase in sexual vigor and speed of ejaculation. These observations on summer infertility in rams and on slow breeding in bulls need further confirmation before thyroid therapy can be recommended as a general corrective procedure.

Antithyroid Drugs, Influence on Growth and Economy of Feed Utilization of Swine and Ruminants

During the past few years, the hypothyroid condition induced by drugs has been studied rather intensively as a possible means of increasing the efficiency of feed utilization. The results of this research indicate that, under favorable conditions, gains in body weight of swine may be greater per unit of nutrient material in individuals given antithyroid drugs than in control animals. *Increased economy* of feed utilization appears to have resulted from the feeding of thiouracil as 0.1 through 0.25 per cent of the ration to fattening pigs that weighed, initially, 114 through 187 pounds for 17.5 to 49 days, inclusive (39, 40, 45, 74, 75, 79, 81, 85). The results of trials in which use was made of individual, paired, trio, and group-feeding techniques led Terrill et al. (75) to conclude that, while thiouracil does not increase rate of gain, it does increase efficiency of utilization of feed and it does reduce feed consumption.

Size of the animal is a factor in determining whether or not the result of thiouracil administration will be favorable. Vander Noot et al. (81) reported that 0.1 per cent of methylthiouracil in the ration increased rapidity of gain in pigs that weighed over 146 pounds, while it resulted in a decrease in rate of gain in pigs that weighed less than 137 pounds at the beginning of the trial. Willman et al. (85, 86) reported that pigs that weighed around 122 pounds, initially, grew not only less rapidly but also less economically on rations that contained 0.1 and 0.2 per cent thiouracil than did their controls. Pigs of one group of 9 individuals that received the smaller dose were continued on thiouracil through a period of 97 days until the animals reached a mean weight of 194 pounds. These thiouracil-fed pigs made mean daily gains of only 0.75 pound, and they did not make their gains as economically as did a control group that reached a mean body weight of 203 pounds in 56 days.

The feeding of goitrogens to *weanling pigs* has led to very unfavorable results. Vander Noot et al. (79) started 41-pound Duroc Jersey and Berkshire pigs on a ration that contained 0.25 per cent thiouracil and kept them on this ration for 97 days. The daily gains of thiouracil-fed pigs were about a third of those made by the controls; however, the experimental animals did gain slightly more economically than the controls. The results of feeding a ration that contained 0.1 per cent thiouracil to 53-pound pigs for 42 days, reported by Beeson et al. (15, 16) were even less favorable. After 6 weeks on thiouracil, the pigs exhibited symptoms of severe hypothyroidism, and it appears unlikely that they could have survived much longer than the end of the six-week period on a goitrogenic ration.

The feeding of goitrogens over extended periods has led to unfavorable results. Willman et al. (85) observed that, while pigs that received a ration containing 0.2 per cent of thiouracil gained more rapidly and economically than the controls during the first 28 days of the experiment, during the fifth week of the trial there was a noticeable drop in feed consumption and in daily gain of the thiouracil-

fed group. Nevertheless, the performance of the thiouracil-fed pigs exceeded that of the controls in total gains and economy of utilization of feed during the first 49 days of the experiment. During the final 9 days of the 58-day trial, gains of experimental pigs were very small. Terrill et al. (75) concluded that the last 4 weeks of fattening constitute the optimum period for thiouracil feeding, but that economy of feed utilization can be increased during periods as long as 6 weeks with little loss in over-all gains.

In several paired-feeding trials in which the feed allowed the controls was equal to that consumed by the experimental animals, gains of the thiouracil-fed animals were much more rapid than those of controls. In an experiment of this type reported by Muhrer and Hogan (44) daily gains of animals fed 0.2 per cent thiouracil for 28 days were 50 per cent greater than control gains, and the experimental animals required 36 per cent less feed per unit of gain than did the controls. However, mean daily gain of controls was only 1.4 pounds per day, which is less than the usual gains of pigs when they are fed ad lib. Terrill et al. (75) reported that in a series of paired-feeding trials, thiouracil added to an adequate ration significantly reduced the feed required for unit gain. When controls were allowed only as much feed as was consumed by thiouracil-fed pigs, the latter grew more rapidly than the former; and when both controls and thiouracil-fed pigs were fed to the limit of appetite, daily gains of the former were somewhat greater than those of the latter group. Willman et al. (85) reported results very similar to these.

In attempts to determine optimum dosage, comparisons have been made of various levels of goitrogen administration. Vander Noot et al. (81) demonstrated that gains were more rapid and at the same time more economical when methylthiouracil was fed at levels of 0.05 and 0.1 per cent than when this drug or thiouracil was fed as 0.25 per cent of the ration. Hale et al. (35) reported that pigs on a 0.15 per cent thiouracil ration gained more economically than those that received 0.25 per cent. Terrill et al. (75) concluded that a concentration of 0.15 per cent was more nearly optimum than 0.1, 0.2, or 0.25 per cent thiouracil in the ration.

It appears evident that the influence of thiouracil on growth of swine may be modified by environmental temperature. Temperature influences may partly explain the results reported by Acevedo et al. (1), who conducted trials during the period between the middle of April and early June at College Station, Texas. Their Duroc Jersey and Hampshire pigs of 114 to 187 pounds body weight responded unfavorably to a ration that contained 0.25 per cent thiouracil fed through a period of 51 days. Efficiency of the thiouracil-fed pigs in the utilization of feed was much lower than that of controls, while daily gains of goitrogen-fed Hampshires were only 37 per cent of the control gains, and mean gain of experimental Duroc Jerseys was 65 per cent of mean gain of the corresponding controls. The influence of environmental temperature upon efficiency of feed utilization, growth rates, and carcass composition of thiouracil-fed pigs has been studied recently by Winchester and associates (88). Pigs fed a 0.15 per cent thiouracil ration for about 28 days were kept in metabolism stalls or confined individually on a concrete floor in rooms maintained at various controlled temperatures. At 50° and 60°F., feed consumed per pound of gain by the thiouracil-fed pigs was significantly lower than that of controls; at 80° and 90°F., with the animals in a turbulent atmosphere, standing or lying on a damp concrete floor, the goitrogen caused very little difference in economy of utilization of feed, while thiouracil-fed pigs kept in metabolism stalls at 90°F. grew even more slowly and less economically than did the controls kept in this environment.

The favorable results that occurred both when thyroprotein was fed to weanling pigs and when goitrogens were fed to fattening swine suggested that a thyroprotein-goitrogen

sequence might result in gains made more efficiently than those obtained with either material administered singly. Hale et al. (35) fed to pigs for 28 days a basal ration to which 0.01 per cent thyroprotein was added, then substituted 0.15 per cent thiouracil for the thyroprotein for the next 35 days. The thiouracil-fed pigs gained more economically than those that did not receive the goitrogen, and of the former, those that had received the earlier thyroprotein treatment gained somewhat more efficiently than those that had not. However, other workers (Perry et al. (52) and Vander Noot et al. (79)) have been unable to demonstrate any advantage of the iodinated protein-goitrogen sequence of treatments over thyroprotein feeding alone.

The effects of antithyroid drugs on the body composition of pigs have been given in a few reports. Muhrer et al. (45) reported 3 per cent more water and an equal percentage less fat in pigs that received a ration containing 0.1 per cent thiouracil than in controls. Terrill et al. (73) found that pigs fed 0.15 per cent thiouracil in the ration retained more nitrogen than did the controls during the second and third weeks of the trial, but that no significant differences were found in the physical or chemical composition of carcasses after 4 weeks of thiouracil ingestion. Determinations carried out recently by Winchester and associates (88) indicate that changes in body composition, due to thiouracil ingestion, may in turn be modified by environmental temperature. The hams of pigs kept for about 28 days at 50°F. on a 0.15 per cent thiouracil ration contained 14 per cent less fat (highly significant), 8 per cent more water (significant), and 6 per cent more protein than hams of pigs kept at these same temperatures on a control ration. While the data on hams of pigs kept at temperatures above 50°F. are not significant, they do show that the hams of thiouracil-fed pigs tended to contain lower percentages of fat and higher percentages of water than the hams of pigs maintained in the same environments but not given thiouracil. There are no data to indicate what effect, if any, these changes in meat composition may have on the keeping and curing qualities of pork products. These could be decisive factors in the acceptability of such products for human consumption.

The question of retention of goitrogenic compounds in the tissues of animals fed antithyroid drugs has been investigated. By a biological method, Pipes and Turner (57) were able to detect about 50 parts per million of thiouracil in pork from pigs fed a ration that contained 0.1 per cent thiouracil but did not detect thiouracil in the flesh of pigs that had received half this dose of the drug during the 28-day trial. Franklin et al. (32) found that muscle of freshly killed pigs that had received 0.2 per cent thiouracil for 34 days contained 60 parts per million of the drug, but in animals killed 24 and 72 hours after the last ingestion of thiouracil the concentration was only 20 and 0.5 parts per million, respectively. Winchester and Scarborough (87) used thiouracil labeled with S^{35} in determinations of elimination rates of the goitrogen. Their figures for thiouracil content of pork muscle one and two days after the last thiouracil was ingested are of the same order as those cited above (32). Franklin et al. (33) also found that thiouracil is excreted rapidly by chickens, and Bezem et al. (17), who used a goitrogen labeled with S^{35}, demonstrated that methylthiouracil is eliminated by fowl with similar rapidity.

In ruminants, the feeding of antithyroid drugs has achieved results similar to those that have resulted from partial thyroidectomy. Thiouracil as 0.2 per cent of the grain ration increased the rate of gain of beef heifers during their first month on this regimen (31, 38). The rate of gain of 790-pound steers was reported by Beeson et al. (14) to be slightly accelerated by the ingestion of 2 to 4 grams of thiouracil per individual daily. Dinusson et al. (27, 28), however, found that 4 grams of thiouracil per head, daily, increased neither the rate of gain

nor the efficiency of feed utilization of beef cattle.

Only a few experiments in which goitrogens have been fed to lambs have been reported, and in none of these was efficiency of feed utilization or growth rate increased (3, 12, 13, 80). Favorable results were obtained, however, by Vander Noot et al. (80) when methylthiouracil was fed to *aged ewes*. Administration of the goitrogen at the 0.05 per cent level but not at the 0.1 per cent level of the ration for 30 days resulted in more rapid and economical gains than those made by control ewes.

Some effects of feeding goitrogens on vitamin A metabolism in calves (Allen et al. (2)), in sheep (Barrick et al. (12)), and in goats (Smith et al. (70)) have been noted. Changes in the fat content of blood serum (Mullick et al. (46)) and in plasma cholesterol (Barrick et al. (11)) in sheep fed antithyroid drugs have also been observed.

Diethylstilbestrol and Testosterone: Effects on Growth of Ruminants and Swine

The administration of sex hormones to ruminants and swine to accelerate rates of gain and increase feed efficiency is a relatively recent development, and no authorization for use of the hormones in these species, on a commercial basis, had been requested of the Food and Drug Administration, Department of Health, Education, and Welfare, up to the time this was written.

Andrews et al. (5, 6) demonstrated that rate of gain and feed efficiency were increased significantly following the subcutaneous implantation of 12 to 24 milligrams of diethylstilbestrol in 70-pound lambs, while carcass quality, determined by official carcass grades, was lowered by the treatment. Results similar to these were obtained by Jordan (36), O'Mary et al. (49), and Pope et al. (58). O'Mary and coworkers found significantly less external fat on stilbestrol-treated lambs than on the untreated animals, and water content of the fat of the treated animals was lower than that of the controls. Growth of bone and muscle, however, was not altered by diethylstilbestrol.

Murphree et al. (47) reported increased rate of gain in suckling ewe lambs that had received a 12-milligram implant of diethylstilbestrol per animal. However, rectal or vaginal prolapse, or both, were observed in 4 of the 5 treated lambs. This same treatment produced increased weight gains in weanling wether lambs through a 56-day period. Perry et al. (51) reported that the implantation of either 12 or 24 milligrams of diethylstilbestrol in suckling lambs on pasture was followed by highly significant increases in rates of gain. This response was obtained in both male and female lambs in experiments that involved 197 individuals. Jordan and Dinusson (37), however, through periods of 91 to 105 days, observed no significant changes in growth rates of male and female suckling lambs that had received 12-milligram implants of diethylstilbestrol.

Yearling beef heifers and steers given 42- to 120-milligram diethylstilbestrol implants gained more economically and more rapidly than controls, but carcasses of treated animals tended to grade somewhat lower than those of controls (4, 8, 9, 28). Clegg et al. (26) reported that a 60-milligram implantation of diethylstilbestrol pellets administered to beef heifers and steers in *feed lots* increased rate of gain in most instances. However, Clegg and coworkers state: "Preliminary data indicate no significant gains in grass-fattened animals." Diethylstilbestrol produces some mammary stimulation in both steers and heifers, and it may cause vaginal stimulation and prolapse in females under some conditions. Andrews, Dinusson, and coworkers (4, 8, 9, 28) found that under feed lot conditions in Indiana no undesirable effects were observed, but when heifers on lush pasture were treated with diethylstilbestrol, excessive mammary stimulation took place. Clegg et al. (26), at the California station, likewise observed that mammary development of heifers was great

enough to be objectionable, and reported that in one group of 80 treated heifers 4 individuals developed prolapse of the vagina. It thus appears that the treatment of heifers with diethylstilbestrol presents problems that do not occur in steers.

The effects of diethylstilbestrol on swine have not been impressive (29, 50, 72, 89). Rate of gain has not been increased and, with the exception of a series of trials reported by Dinusson et al. (29), increased efficiency of feed utilization was not observed. Genitals of both females and barrows were stimulated, and prolapse of the uterus was reported by Dinusson. However, Braude (22) reported an increase in rate of growth and efficiency of feed utilization in pigs that had received both diethylstilbestrol and iodinated protein, and Murphree et al. (47) reported that pigs on pasture with tankage and ground barley fed free-choice, when implanted with 12-milligram pellets of diethylstilbestrol weighed 20 per cent more than controls 72 days after treatment, but only 4 per cent more than controls 99 days after implantation.

Studies have been made of the influence of the male sex hormone, testosterone, on rate of gain and efficiency of feed utilization in beef heifers and steers and in lambs. Dinusson et al. (28) observed a transient effect of testosterone in oil solution on growth of heifers. Bogart et al. (20) injected 3 beef heifers and 3 steers with 1 milligram of testosterone weekly per kilogram of body weight and observed an increased rate of gain and improved efficiency of feed utilization in both females and steers. Andrews et al. (7), however, observed that 180 milligrams of testosterone pellets had little effect on growth of cattle. In one experiment with wether lambs, a 10-milligram testosterone implant improved carcass grade, feed efficiency, and rate of gain (Andrews et al. (66)), while O'Mary et al. (49) and Pope et al. (58) found testosterone to be without effect on lambs under the conditions of their experiments.

Summary and Recommendations

Although two new-drug applications for permission to manufacture iodinated casein compounds have been granted by the Food and Drug Administration, Department of Health, Education, and Welfare, present evidence hardly justifies their use in feeds for beef cattle, sheep, or swine to increase rates of gain or efficiency of feed utilization. The most successful use of thyroprotein has been obtained with young growing pigs, but even in young swine the results have been variable and the effects of several factors that may influence results are not well defined.

Reports of the successful use of thyroprotein to improve summer infertility in sheep or to increase sexual activity in bulls need further confirmation.

The use of goitrogens in swine husbandry must be considered to be still in the experimental stage. Whether or not the goitrogens presently available, used in such ways as have been tried to date, are suitable for use in pork production is a question that has not received a final answer. However, some goitrogens have produced significant increases in efficiency of utilization of feed without markedly decreasing rates of gain when they have been employed during the last 4 weeks of the fattening period. Administration of goitrogens for more than 6 weeks usually has depressed growth rates significantly. The possible danger to consumers of pork and pork products from retention of thiouracil is recognized, but this danger is negligible if goitrogen feeding is avoided during the last 3 days prior to slaughter.

In those experiments in which carcass analyses were made, it was found that goitrogens had not increased fatness of swine during a 4-week fattening period. The trend was, rather, in the opposite direction. The carcasses of thiouracil-fed pigs have been found to contain less fat but more water and protein than control pigs. The effects of these changes in carcass composition on market grade and on the keeping and curing qualities

of pork have not been determined. They could be decisive factors in the acceptability of such products in some markets.

One new-drug application for permission to incorporate thiouracil in commercial mixed feeds for poultry and swine has been granted by the Food and Drug Administration, Department of Health, Education, and Welfare.

Consistent improvement in either rates of gain or efficiency of feed utilization has not accompanied the feeding of goitrogens to ruminants and, in addition, feed intake has tended to decrease when goitrogens have been used, possibly because of the bitter flavor of many of the compounds. It appears that the goitrogens available at the present time do not offer much promise of usefulness in connection with the feeding of ruminants.

Whether or not commercial use will be made of diethylstilbestrol and testosterone in meat production will depend upon the economic advantage that may be derived from such use, and upon whether or not further research demonstrates their safety so far as human consumption of products of the treated animals is concerned. Experiments have proved that stilbestrol increases rate of gain and efficiency of utilization of feed in cattle and sheep. Apparently because of reduced subcutaneous fat and changes in the pelvis, carcass grades of stilbestrol-treated animals have been consistently lower than those of controls. Undesirable mammary development and, in heifers, prolapse of the vagina have occurred with stilbestrol administration under some conditions. While some beneficial effects have accompanied testosterone administration, these are suggestive of future possibilities and cannot be regarded as being conclusive. It has not been demonstrated that significant changes in rate of growth, efficiency of utilization of feed, or carcass quality have been produced by sex hormone treatments of swine.

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THE USE OF ESTROGENS TO STIMULATE UDDER DEVELOPMENT AND LACTATION IN CATTLE AND GOATS

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A large amount of experimental evidence has indicated that mammary growth and lactation are controlled to a considerable extent by the secretion of steroid hormones from the ovaries and adrenals and by the secretion of pituitary hormones from the anterior lobe of the pituitary gland. The thyroid secretion and possibly secretions from other glands may also participate in these processes. Several excellent recent reviews (8, 9, 10, 34, 35) summarize the literature and discuss in detail the endocrine or hormonal aspects of mammary growth and lactation. Reviews by Nelson (32), Turner (44), and Folley (7) cover the older literature on the subject.

The possible applicability of the use of estrogens to induce udder growth and lactation in domestic animals was first indicated by de Fremery (4, 5). De Fremery showed that marked udder development in goats could be obtained when estradiol benzoate was applied by inunction to the udder. When diethylstilbestrol became available, numerous experiments with goats and cattle were undertaken. Other synthetic estrogens were also tested as they became available. Studies in the goat have been conducted by Turner and his associates (23, 24, 25, 26, 30, 31) in America and by Folley and associates in Britain (14, 15, 17, 20). Similar and much more extensive studies with cows have been conducted by Walker and Stanley (45, 46), Reece (37, 38, 39), Petersen et al. (36), Folley and associates (11, 12, 13, 14, 16, 18, 19), Marshall et al. (27), Spriggs (42), Cowie (1), Parkes and Glover (33), Lawson et al. (22), and Hammond and Day (3, 21).

Methods of Administration

The estrogens have been administered in a variety of ways. These include injection and implantation techniques, percutaneous application by inunction of the udder area with ointments containing stilbestrol, and administration by mouth.

Oral administration does not appear to be practical in either goats or cattle. Lewis and Turner (25) reported that approximately 20 times the injected dose was needed for a comparable effect when stilbestrol was given orally, and Mixner et al. (31) report that 100 times the injected dose is needed for comparable lactation inhibiting effects. In cattle, the relative ineffectiveness of orally administered estrogen has been noted by Folley et al. (12, 16). The large amounts of synthetic estrogens which would presumably be necessary to elicit adequate responses when they are fed by mouth would therefore make this procedure costly and eliminate it from consideration as a practical procedure.

Percutaneous administration by direct application to the udder has likewise been unsuccessful in cattle, although this has been tested on only a few animals (15, 16, 18). In goats, this form of application has been more successful; 10 milligrams of stilbestrol applied in the form of a one per cent ointment three times weekly caused mammary development and lactation in virgin goats (15, 17, 25, 26). A dosage of 0.25 milligrams per day is effective when injected subcutaneously, but percutaneous administration is only about $\frac{1}{20}$ as effective, even in goats, as subcutaneously injected stilbestrol. Lewis and Turner (25) indicated that the ratio of effectiveness of subcutaneous to percutaneous stilbestrol was about 1:16.

The most adequate forms of administration of estrogen are by injection in oily solution or by implantation of pellets subcutaneously. With goats, 0.25 milligrams per day by injection appears to be an adequate dose (23, 24, 25,

30, 31) for udder development and lactation in unbred goats. While considerable variation exists as to the time of response following injection, and indeed in the type of response obtained, a 60-day period of injection would appear to be desirable. There is apparently little advantage in prolonging the period over which injections are given, even in goats which do not respond during this 60-day period.

In cattle, mammary growth and lactation have been induced following estrogen injections by Walker and Stanley (45, 46), Reece (37, 38), and Marshall et al. (27). The data of Marshall et al. suggest that dosages of 50 to 60 milligrams per week for 3 to 15 weeks are adequate, although 15 to 20 milligrams weekly over 10 to 15 weeks (37, 38) has also been shown to be an effective dose. Results from the injection of single large doses of several esters of stilbestrol were disappointing (33). Treatment by injection, however, although effective both in goats and in cows, is time-consuming and not particularly suitable to farm conditions.

Implantation of pellets seems to be the most practical form of treatment. This technique has not been tested extensively with goats. Implantation of 0.4 grams of stilbestrol or hexestrol for 119 days resulted in mammary growth and lactation in four virgin goats (14). Lewis and Turner (25) obtained positive responses in goats by implanting 100 milligrams of stilbestrol. Much more extensive studies with this form of treatment have been made with cattle (3, 11, 19, 21, 42). Implantation is effected by making an incision through the skin in the neck region or just behind the shoulder. A deep pocket under the skin is then made by blunt dissection, the pellets are placed in position and the skin incision closed. Not all the estrogen is absorbed, and it is recommended that the unabsorbed portions of implants be removed between 60 and 100 days after implantation (3, 21, 42), the time depending on the response obtained. The implantation of 2 to 5 large pellets containing a total of 2.0 to 5.0 grams of estrogen, all factors considered, appears to be the most satisfactory dose. There is no exact relationship between dose and response. Folley and Malpress (11) suggest that absorption rates from 5 to 12 milligrams daily should be attained. Stilbestrol and hexestrol are equally effective.

Effects on Udder Growth and Lactation

The effects of estrogens on established lactation, in dosages that produce discernible effects on milk flow, are inhibitory both in goats and in cows. This has been noted by Folley (6, 16) and Reece and Murphy (39) for cows and by Lewis and Turner (23) and Mixner et al. (31) for goats. Marked decreases in milk production occur as the result of estrogen treatment. Reece and Murphy (39) noted the production of flaky milk in cattle treated with stilbestrol. The stilbene derivatives or other estrogens are therefore contraindicated as agents to increase established lactation.

Similarly, attempts to induce lactation in dry sterile cows and dry goats by estrogen treatment have in the main been quite disappointing (11, 14, 19, 20, 21, 26, 27, 42). A summary of data from these sources shows that more than 20 per cent of such cows do not respond at all, and an additional 50 to 60 per cent produce less than 20 pounds of milk per day and a total of less than 4000 pounds in the induced lactation. Table 1 summarizes these data.

Recently Meites et al. (29) have used a combined estrogen-progesterone treatment to induce lactation in dry cows. More adequate lactation responses have been obtained by these workers than have been obtained by others who have used estrogen only. More extensive data are needed to establish the general applicability of this form of treatment.

The effect of estrogens to stimulate udder growth and induce lactation in castrate or sterile heifers has been studied rather extensively (3, 11, 12, 19, 21, 27, 33, 38, 42, 45, 46). Here again the results have been quite variable.

A tabulation of data from the above sources presented in Table 1 shows that about 16 per cent of such animals did not respond at all, and an additional 60 per cent produced less than 20 pounds of milk daily and less than 4000 pounds in the complete lactation. Only 1.5 per cent produced more than 30 pounds daily and only 3.5 per cent produced more than 7000 pounds of milk in the complete lactation.

The responses of virgin or unbred goats to estrogen treatment have likewise been quite variable (14, 17, 23, 26, 30, 31). Data on complete lactations are lacking and results are usually expressed in terms of maximal daily lactation. Daily yields of 4.3 and 5.3 pounds have been obtained. Yields of 1.5 to 3.0 pounds daily have been more frequently observed and about 25 per cent of treated goats give negligible responses. In unpublished work done at the Bureaus of Animal and Dairy Industry, U. S. D. A. (40) in which 45 yearling does were injected with stilbestrol, 9 does produced a total of less than 50 pounds of milk, 10 between 50 and 100 pounds, 12 between 100 and 300 pounds, and 3 between 300 and 500 pounds in a complete induced lactation. Eleven does did not produce measureable quantities of milk. Maximum daily production ranged from 0.25 to 4.0 pounds.

TABLE 1

LACTATION RESPONSES OF DRY COWS AND HEIFERS TO ESTROGEN TREATMENT

	Maximum recorded daily production (pounds)				Total production (pounds)			
	0	0–20	20–30	30–40	0	0–4000	4–7000	7–10,000
Percentage of treated dry cows....	22.2	51.3	27.0	0	22.2	63.8	12.1	3.8
Percentage of treated heifers.....	16.7	64.1	17.8	1.5	16.7	57.3	22.5	3.5

Attempts to induce lactation in freemartins have resulted in almost uniformly complete failure. Amounts of milk obtained have seldom exceeded 2.0 to 3.0 pounds per day. Only a few cases are reported in the literature.

The variability in these responses may be due to the fact that an abnormal type of udder development appears to result from estrogen treatment of goats and heifers (10, 30, 43). A more normal type of tissue resulted when progesterone was given in addition to estrogen. The lactation responses of heifers and goats treated with both progesterone and estrogen appeared to be improved (2, 28, 29) in comparison to those obtained when estrogen alone was administered, but more extensive data are needed on this point.

Since it is evident that pituitary hormones are important factors in the initiation and maintenance of lactation, attempts to improve the lactation response to estrogens by injecting pituitary hormones during or following estrogen treatment have been made (14, 20, 25, 45). While goats appear to respond to this combined treatment better than cattle, the responses generally are still inadequate, and it is by no means certain that responses to estrogen will be improved by injections of pituitary hormones or that the variability in estrogen response is due to deficiencies of pituitary secretion.

The composition of the milk produced during induced lactations under the conditions of estrogen treatment noted above is in general normal. In goats, Folley et al. (17) noted that at first the milk was colostral in type and characterized by low casein and high globulin content. A gradual change to milk of normal composition then occurred, although this change was slower than occurs in a normal lactation. A tendency for the milk to revert to the colostral type was noted in one lactation during a period when estrogen treatment was apparently excessive. The milk produced by heifers in an artificial lactation was similarly

colostral in character at first (13, 21). It gradually changed to milk of normal composition, the rate of change being roughly proportional to the rate of increase in yield. Generally, the milk was of normal composition when production reached about 5 pounds per day.

The effects of administered estrogen on milk composition of lactating cows has been noted by Folley et al. (6, 16) and by Spielman et al. (41). Dosages of estrogen which caused no or only transient decreases in milk yield increase the milk solids and fat percentage of milk. This effect was also seen with dosages which caused marked decreases in milk yield. Reece and Murphy (39) have noted the appearance of flaky milk in cows given estrogen in amounts sufficient to depress milk production. This "enrichment effect" unaccompanied by decrease in yield was in general produced by small amounts of estrogen. Larger doses caused inhibition of secretion. Optimal dosages and methods of administration for the enrichment effect only have not been determined.

The excretion of estrogen in the milk of treated cattle has been studied by Lawson et al. (22). Small amounts were found in milk, but none of the results suggest that sufficient quantity was present to be harmful to the human.

Miscellaneous Effects

Reproduction. Observations on the reproductive activities of cattle during and following treatment with estrogens have been noted by several investigators (3, 11, 21, 27, 42). During treatment animals were almost constantly in heat in most instances and when running loose with others engaged in a good deal of coital mimicry. Their behavior rather closely resembled that of cattle with nymphomania. Spriggs (42) noted that the behavior of treated cattle appeared more normal if they were stalled separately and not allowed to run with other cattle. Examination indicated that the ovaries were small and inactive and that the estrus cycle was absent. While many of these cattle would accept service, they were sterile during the treatment period.

Following treatment, estrus cycles were reestablished after variable periods of time—usually one to three months. When bred, these animals reproduced at about the rate existing before treatment. While it appears that estrogen did not impair subsequent fertility, it did not improve it. Similar observations have been made on goats (25, 40).

Folley et al. (16) have observed abortions when estrogen was given to pregnant cows.

Physical Abnormalities. During treatment with estrogen, marked changes in pelvic anatomy may occur (11, 21, 27, 42). Relaxation of the pelvic ligaments and raising of the tailhead occurred frequently. Dislocations and fractures occurred frequently. Folley et al. (11) noted an incidence of pelvic fractures of about 20 per cent. These occurrences were reduced if the animals were isolated (42). Cowie (1) made a detailed study of the fractures occurring in estrogenized cattle. Meites et al. (28) have indicated that many of those undesirable side effects of uninhibited estrogen activity may be prevented if progesterone is implanted during the course of estrogen treatment.

Summary and Recommendations

Lactation can be induced with estrogenic materials in 70 to 80 per cent of unbred heifers, dry cows, and dry goats. Less than 50 per cent of such animals produce commercially profitable quantities of milk. Administration of estrogens by implantation is the least costly and most useful method of treatment.

Undesirable side effects of estrogen treatment occur frequently. Persistent coital mimicry makes treated cattle bothersome to others in the herd. Treated cattle are sometimes excitable and difficult to handle and may require isolation during treatment. Pelvic abnormalities and fractures occur frequently.

Because of the uncertainty of response, the relatively poor yields obtained, and the bother-

some nature of treated cattle and danger of crippled animals, induction of lactation with estrogens is not at present recommended as a general practice even in animals which would otherwise be non-producers.

Further research may show that treatment with both progesterone and estrogen will produce more consistent lactation responses and will prevent many of the undesirable features which are characteristic of estrogen administration to dairy animals. There are insufficient data to recommend this procedure at present.

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THE USE OF THYROPROTEIN FOR MILK PRODUCTION

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Many reasons have been advanced for associating the metabolic activity of a cow with the amount of milk and milk fat secreted. Graham (24, 25) altered the thyroid status of cows in an effort to cause variations in milk production and also presumably altered the metabolic rate. These studies initiated the modern interest in the subject of thyroid status and milk production in dairy cattle.

Early literature dates to 1896, when the administration of thyroid gland material to normal individuals increased the milk production of cows and women (29). These original investigations seem not to have been followed up, although medical literature contains periodic reports concerning thyroid feeding and increased milk yield of women (30, 31).

Thyroidectomy of cows and goats has usually reduced the amount of milk produced, and yield has been increased by giving thyroid material (25, 69). Removal of the thyroid also reduces growth, which is corrected or restored by feeding thyroprotein (62, 71). Administration of goitrogens has not given conclusive changes in milk production, as they also affect feed intake (65, 79).

Following the limited number of results showing that thyroid gland feeding increased milk yields, many investigators injected thyroxine and obtained similar results (22, 27, 28, 36, 37, 49, 51, 69). Its high cost and the necessity of injection (at that time) limited thyroxine to experimental use. The practical aspect of increasing milk production by thyroid material was well realized but necessitated a cheap source of thyroxine or thyroid-active materials.

The introduction of biologically active iodinated casein (thyroprotein) by Reineke et al. (58, 61, 62) and of synthetic L-thyroxine (15, 17) has fulfilled these requirements. Little work has been reported to date on the effects of synthetic L-thyroxine on milk production (5). Thyroprotein is now made on a commercial scale and is available to feed manufacturers for inclusion in feeds. In this form it is available to farmers.

The Food and Drug Administration of the United States has approved the use of thyroprotein or feeds containing thyroprotein for feeding to dairy cows. In Great Britain the use of thyroprotein or thyroxine in cattle feeds is authorized for experimental purposes only. The Pure Bred Cattle Association of the United States passed a rule in June 1949 prohibiting the use of thyroprotein for cattle which are on official test. The Dairy Herd Improvement Associations in the United States do not prohibit the use of thyroprotein but have requested that its use during test periods be reported.

Effect of Thyroprotein on Milk Production and Composition of Milk

Following the first demonstration (13, 58, 61) that iodinated casein would increase milk production, many investigators have confirmed and extended the original observations. A large series of rather short-term trials have been reported in which the iodinated casein was fed for a few days or weeks (1, 7, 9, 14, 23, 32, 52, 53, 62, 66, 85). The changes in milk production which have been obtained have been extremely variable. After feeding thyroprotein, the milk production increase has ranged from an increase of 16 pounds per day down to a small decrease over a period of one month. These changes have varied from a decrease of 8 per cent to an increase of 61 per cent. An average group of cows may be expected to average from 3 to 8 pounds more milk per day for a period of one month, or an in-

crease of about 8 to 25 per cent, as a result of proper feeding of thyroprotein. The maximum increase occurred between 5 and 60 days after initiating thyroprotein feeding, and the level of production remained above pre-treatment level for 0 to 168 days. Several factors may have been responsible for this variability. These and other effects are discussed later.

Several reports have been concerned with the effects of feeding thyroprotein for the major part of a lactation or for successive lactations (35, 41, 44, 45, 53, 55, 56, 57, 72, 73, 76, 77, 78, 79, 80). As in the shorter trials, an increase in production has usually been observed after iodinated casein was added to the ration in an adequate dosage. The increase was of the same magnitude as in the shorter trials.

The persistence of this increase over the entire lactation period has been variable and was largely dependent on level of feed intake (21, 41, 53, 78, 79, 80). When cows were fed in the usual manner, i.e. according to body weight and milk production, the increase was maintained for a relatively short time (4 to 5 weeks); after this transient increase, a more rapid than normal decline in milk production occurred. After mid-lactation, the level of milk production was below that of control cows. When feed intake was increased in excess of apparent requirements, good persistence was observed (78, 80). There is evidence to suggest that even with extra feed the total lactational effect of thyroprotein feeding is small or nil, since after mid-lactation the milk production of cows on extra feed alone was more than that of those fed extra feed and thyroprotein. (21, 53, 72, 78, 80). Low persistence also was observed when low dosages combined with a small increase in feed intake were given (41).

The question has not been satisfactorily answered as to whether any given cow or group of cows will produce more milk, or produce it more economically, when receiving thyroprotein during the major portion of a lactation compared to possible production under the same conditions without any thyroprotein.

In experiments that covered several lactations, the evidence suggests that milk yields in succeeding lactations may be somewhat below the normal expectations. When all lactations were expressed on a mature equivalent basis, thyroprotein-fed cows did not maintain the same level of production over succeeding lactations, whereas control cows did (57, 77, 78). Both fat test and milk yield were reported to be less than expected during the first 50 days of a lactation which followed a previous lactation in which thyroprotein was fed (56, 77, 78).

Several investigations (7, 9, 12, 23, 32, 53, 61, 66, 79, 85), have shown that a marked decrease in milk production to below normal levels occurred when thyroprotein was removed from the ration. This reduced the net increase in milk production due to iodinated casein feeding. In an effort to minimize this sudden drop in milk production, Blaxter (9) fed extra feed to one group when iodinated casein was withdrawn, and to another group he gradually decreased the amount of iodinated protein. The latter treatment prevented the precipitous sudden drop, but the total production of the two groups was the same over a six-week experimental period. Neither treatment could be regarded as successful, but the slow withdrawal is recommended because of lack of a better method. In one experiment, no decrease in milk production was found when cows were placed on good pasture after the sudden removal of thyroprotein (81).

The effect of thyroid-like stimulants on fat content of milk has been extensively investigated (1, 3, 7, 8, 9, 14, 22, 24, 27, 28, 49, 51, 52, 53, 56, 58, 59, 67, 69, 73, 80, 85, 86). Most investigators noted a variable and sometimes small increase in fat test, while only two (32, 41) failed to find any increase. The average fat per cent for the first post-experimental month was about 0.2 to 0.4 per cent above the pre-experimental month, after which any effect was totally or partially offset by the normal increase in fat per cent which occurs as lactation progresses (53, 67, 79, 80).

Investigations on other milk constituents indicate insignificant or no changes in 1) solids-not-fat content (1, 3, 5, 6, 7, 8, 14, 22, 27, 36, 41, 49, 51, 69, 70, 85); 2) lactose (1, 3, 36, 37, 51, 69); 3) various nitrogen fractions (1, 3, 14, 32, 36, 41, 49, 69, 70, 86); 4) ash (1, 3); 5) carotene and vitamin A (6, 32, 39); and 6) total thiamine (6, 32, 39). The feeding of thyroprotein preparations has produced a decrease in the ascorbic acid content of milk (6, 14, 85, 87) which was probably due to the inorganic iodine ingested (6, 85) since thyroxine administration produced only an insignificant change (6). A decrease in the level of casein and urea nitrogen (3, 14) and riboflavin (6, 32, 39) was observed. An increase in the level of iodine (6), niacin (39) and relative phosphatase values (6, 7, 8, 22, 48) was reported.

The lactating mammary gland has been shown to be relatively impermeable to administered thyroxine, and milk from cows fed thyroprotein has been safely fed to humans and laboratory animals (16, 18, 34, 43, 63, 64).

The above results indicate that when thyroprotein is fed under optimal conditions an increase of 10 to 25 per cent in milk production for a period of 4 to 10 weeks may be expected. When this increase is prorated over the whole lactation the net effect may be small because of decreased persistence in late lactation. Moderate increases in the fat content may accompany the increase in milk production.

Factors which Affect the Lactation Response to Thyroprotein

The largest single factor affecting degree of response was the rate of the cow's feed intake, especially when the trials were conducted over longer periods. The importance of this factor was mentioned in the foregoing section. This point was first specifically mentioned by Moore (44) although in the original work of Graham (25) the addition of extra food checked the rapid decline in milk production during the 19th to 28th weeks of the experiment. Other investigators (9, 32, 80) also showed the necessity of extra feed for obtaining optimal results.

Without extra nutrients and with continued thyroprotein feeding, the level of production exceeded that of the control cows (or the expected level of the thyroprotein-fed cows) for only 2 to 3 months, after which it was below the expected level. Simultaneous feeding of extra feed and thyroprotein gave a sustained increase for the entire lactation above levels expected when nutrients were fed at normal rates. The difference for the entire lactation between extra feed alone and extra feed combined with thyroprotein was not large; after 3 to 4 months the production of cows receiving thyroprotein and extra feed was less than that of cows receiving only extra feed (78, 80). In general, the largest increase in milk production accompanied the largest increase in feed intake. Herds of cows under poor management practices gave smaller responses than those under good management (9).

A feed intake of at least 125 per cent of the cow's maximum requirement has been required to obtain an optimal increase in milk yield. Smaller feed intakes or intakes of 125 per cent of the cow's minimum requirement have given a suboptimal increase in milk production (9, 14, 23, 41). The feeding of an extra 3 pounds of grain mix containing thyroprotein in addition to the regular ration, which is recommended by the manufacturers of thyroprotein-containing concentrates, usually does not increase the cow's feed intake to 125 per cent of maximum requirements.

Most investigators have observed a relationship between the milk production increase and the amount of the thyro-active material fed (5, 7, 23, 41, 60, 83). For example, an increase in production of 17, 22, and 33 per cent occurred when 15, 20, and 30 grams, respectively, were fed to three groups of cows (7). In some cases, small differences in dosage rate gave practically no difference in response (73, 80). Evidently it is possible for other factors to overshadow the effects of dosage level.

It has been observed that older cows gave larger responses in milk production than did younger cows (9, 14, 79). The breed of the cow has not been a significant factor in and of itself (7, 9). However, when the same amount of thyroprotein was given to cows of different sizes (and breeds) the smaller cows gave a proportionally larger response in milk production. In order to obtain a more uniform response, thyroprotein should be fed in proportion to body weight, or theoretically in proportion to metabolic body size, as resting basal metabolism was linearly related to dosage expressed in milligrams per kilogram to the 0.73 power (12).

The stage of lactation and the inherent producing ability of cattle affect the responses obtained by feeding thyroprotein. In early trials, thyroxine injection and thyroid gland feeding gave only a small increase in milk production during the late and early part of the lactation period (25, 27, 51). Cows in the late stage of lactation have shown smaller responses to iodinated protein feeding than those in other stages of the lactation period (7, 9, 13, 26). The response in pounds of milk was usually related to the milk yield, but when expressed on a percentage basis the figure may favor the lower-producing cow (9, 79). The initial yield of milk during the lactation was related to the response when thyroprotein was given in mid-lactation; in other words, high-producing cows respond more than low-producing cows (9, 72, 79). Individuality of the cow was another factor used to explain observed differences in response (3, 9, 80). It is not possible to make a good cow out of a poor cow by feeding thyroprotein.

As a result of the above considerations it is recommended that cows be fed 1.5 grams of thyroprotein per 100 pounds of body weight, together with extra nutrients. In practice, 3 pounds of a grain mixture containing 15 grams (5 gm/lb) of thyroprotein fed in addition to the cow's usual feed allowance will qualitatively satisfy these conditions. Thyroprotein feeding should not be started until after the first 50 days of lactation nor in the terminal stages of lactation.

Miscellaneous Effects of Feeding Thyroprotein

Adequate experiments have not been performed to study feed input-milk output ratios under practical conditions of thyroprotein feeding. In experiments to date, when body weight losses were not considered, the cows given thyroprotein produced more milk per pound of Total Digestive Nutrients (T.D.N.) consumed in both short (1, 23, 66, 81) and long term trials (78). The variability among normally fed and thyroprotein-fed cows was large. When the usual correction for body weight change was applied, milk output per pound of T.D.N. consumed was unchanged in two short term trials (66, 81) and decreased in another (23), but was not significantly changed in a long time trial (80). However, when thyroprotein was fed for several successive lactations, the efficiency was decreased after the first lactation (78).

Basal heat production was elevated by about 30 per cent in milking cows (83) and calves (46) when given thyroprotein at approximately 2.5 gm/cwt. On the basis of increased feed intake and increased milk production, these two studies showed that feed intake per unit of extra milk production was markedly above normal. In practice, the dairyman must weigh all feed consumed against all milk produced when considering the economy of feeding thyroprotein.

Experimental evidence indicates that dry matter digestibility was reduced in two sheep given large doses of thyroprotein. The increased dry matter excretion was accompanied by increased water excretion via the gut (10, 49). Diarrhea, or more liquid feces, was observed in animals fed thyroprotein (9, 10, 20, 49, 79); an increased rate of passage of feed through the gut was also noted (10, 40, 49, 76).

Nitrogen balance of cows was negative when

feed intake was restricted but was positive when feeding was liberal after a daily injection of 10 milligrams of thyroxine (10, 49, 83). Creatine excretion was only temporarily increased (10, 49).

The effect of feeding thyroprotein on body weight of cattle depends on the degree of stimulation, the feed level, length of the feeding period, dosage given, and individuality of the cow. Moore and co-workers (44, 80) and Blaxter (7) found that the large weight losses were preventable by extra nutrient consumption. Some investigators noted body weight losses even when extra nutrients were given (1, 14, 23, 41). In practice, cows fed 3 pounds of commercial feed containing thyroprotein, in addition to the usual feed allowance, may show excessive decreases in body weight, probably because this amount of extra feed does not increase the total intake to 125 per cent of the cow's requirement. Cessation of thyroprotein feeding results in a rapid body weight increase (13, 79, 80). Thyroprotein feeding or thyroxine injection to young dairy animals has resulted in reduced body weight gains (42, 48, 54, 79), and T.D.N. consumed per pound of body weight gain was increased (79).

Thyroxine or thyroprotein administration has caused no significant changes in blood levels of hemoglobin, hematocrit, calcium, inorganic phosphorus, serum ketones, serum phosphatase, plasma CO_2 combining power, ascorbic acid, carotene, or vitamin A in cows and calves (2, 8, 10, 11, 14, 20, 22, 23, 32, 42, 47, 79, 87). Blood sugar concentration tended to be increased (8, 11, 20, 23, 37, 42, 47, 51, 69) and relative serum phosphatase values (8, 22) were increased. A decrease in blood levels of total nitrogen, cholesterol, and urea and in specific gravity was found (14, 20, 37, 42, 48, 51).

The results of Aub et al. (4) are often quoted as showing an increased calcium excretion of rats fed thyroid. Later work has shown no specific catabolic effect on bone calcium if the dietary calcium intake was adequate (68). The calcium balance became more negative in 5 of 6 cows injected with thyroxine (50), and excessive doses produced a marked negative calcium and phosphorus balance in sheep (10). Unspecific changes in the bone were reported (20, 48). Dairy cows have received thyroprotein during each of six successive lactation periods with no apparent skeletal changes. The ash content of rib ends, and X-rays of ribs and the metacarpus, of nine cows fed thyroprotein for one to four lactations and of two control cows showed no differences (79). It appears unlikely that thyroprotein fed at the recommended levels for 100 to 300 days per lactation will cause any significant change in calcium and phosphorus metabolism.

Studies on cardiovascular and respiratory activity have shown that the extent of the heart rate increase caused by feeding thyroxine or thyroprotein was dependent on the dosage given (5, 7, 8, 11, 41, 51), the original heart rate (7, 8, 11), and the level of nutrients consumed (74, 80). Changes in heart rate and milk production were positively correlated.

Thyroprotein feeding has caused some abnormal heart sounds (8, 9, 11, 20, 33, 82). Electrocardiograms of sheep (47, 51), goats (51), and cows (20, 51, 76, 82, 83) have shown little change from thyroprotein feeding except for a possible prolonged Q–T interval or an occasional extra systole (20, 82).

Respiration rates were usually increased (1, 7, 8, 9, 11, 12, 14, 22, 23, 32, 45, 51, 55, 72, 85, 86, 87) or variably affected (22, 79, 87) when thyroxine or thyroprotein was given. Body temperature was increased (7, 8, 11, 22, 23, 51, 66, 67) or remained unchanged with great variability (1, 14, 22, 37, 66, 69, 79). Since body heat production is increased with thyroprotein (12, 46, 83), it is reasonable to expect respiration rate and body temperature to vary in relation to the existing environmental conditions and the possible increased heat stress caused by the administered thyroprotein. Thyroprotein fed to cows in high environmental temperatures has given sub-

optimal responses in milk production along with reduced feed intake (8, 14, 23, 67, 79). The feeding of excessive amounts of thyroprotein produced an involvement of the heart and lungs of sheep (11). Smaller amounts have produced no noticeable effects in cows (48, 79) except that the adrenals, ovaries, and thyroid gland were atrophic (48, 72, 79) and the latter contained a reduced amount of thyroxine (48).

An apparent increase in size of the udder has been observed in heifers, dry cows, and milking cows fed thyroprotein (14, 19, 20).

Cows and goats have been given combinations of thyroprotein and estrogens in an effort to induce or increase milk production. The actual results have not been so promising as the theory (19, 38, 75, 84).

No effect on general health or frequency of abortions in cattle fed thyroprotein was found (9, 79). The number of services required per conception was not altered in some cases (41, 73, 79) and was increased in others (20, 35, 57, 76, 79).

Calves from cows fed thyroprotein have appeared normal at birth (41, 57, 66, 76, 78, 79). A high mortality rate was reported in calves after birth when the cows received thyroprotein for 200 to 300 days (57, 78) but shorter periods of administration apparently have not affected calfhood mortality (8, 35, 41, 66, 73).

Summary and Recommendations

The feeding of thyroprotein to dairy cows will usually increase the level of milk production by 10 to 25 per cent. This increase can be maintained for 3 to 5 months where good feeding and management are practiced. The fat test of the milk will usually be increased 0.2 to 0.3 per cent and this increase may be only temporary.

Extra nutrients, about one fourth more than the cow's *maximum requirements*, must be fed with thyroprotein in order to obtain a satisfactory sustained response in milk production and to prevent large decreases in body weight. In herds where cows are fed near or below *minimum requirements*, less satisfactory responses will be obtained, and in such herds it will be more profitable to increase the general level of feeding with ordinary feedstuffs rather than with the more expensive feeds containing thyroprotein.

There was no apparent gain in efficiency of milk production when thyroprotein was fed, and when it was fed for most of the lactation period during successive lactations there was a decrease in efficiency of milk production in the later lactations. Similarly, the increase in total milk per lactation may be negligible when thyroprotein is fed for 200 or more days of the lactation period.

There is little evidence that the feeding of thyroprotein produces changes of practical importance in the health of cattle or in milk and blood composition, except that an increased mortality of baby calves from dams fed thyroprotein during most of pregnancy has been noted. This latter observation needs further confirmation and may not be of importance if thyroprotein is fed for only short periods of time. No danger to human health appears to exist from the consumption of milk produced under these conditions.

The available data suggest no definite economic advantage of feeding thyroprotein to dairy cows under most farm conditions. It appears more desirable for the dairyman who raises his own herd replacements to refrain from using thyroprotein, especially if the calf mortality observations are confirmed. It may, however, be advantageous to use thyroprotein in well-fed commercial herds in which maximum production per cow is emphasized and in herds during periods of short milk supply where this is permitted by law and where other regulations do not prohibit its use. It probably should not be fed for periods longer than 90 to 120 days and not during the first 50 days of lactation or in the terminal part of lactation.

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